(iv) a survivin gene-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions of any sequence of (i) or (ii) at its 5' or 3' end; and

(4) diagnostic kits for diagnosing a neoplastic, hyperplastic, cytologically dysplastic and/or premalignant cellular growth or proliferation in a human subject, kit comprising:

(a) any of the oligonucleotide primers or primer sets cited above; and

(b) instructions for using the primer set in diagnosing a neoplastic, hyperplastic, cytologically dysplastic and/or premalignant cellular growth or proliferation in a human subject.

USE - The method is useful for detecting abnormal cellular proliferations including neoplasms. In particular, the method is useful for detecting neoplastic, hyperplastic, cytologically dysplastic and/or premalignant cellular growth or proliferation. Specifically, the neoplastic growth is a carcinoma, sarcoma, lymphoma, mesothelioma, melanoma, glioma, nephroblastoma, glioblastoma, oligodendroglioma, astrocytoma, ependymoma, primitive, neuroectodermal tumor, atypical meningioma, malignant meningioma, or neuroblastoma. The hyperplastic and/or cytologically dyplastic cellular growth or proliferation is benign prostatic hyperplasia/dysplasia or cervical hyperplasia/dysplasia (all claimed).

ADVANTAGE - The method is a highly sensitive, accurate and non-invasive diagnostic test useful in screening for a broad range of abnormal cellular proliferations. The method is capable of detecting early urinary tract neoplasms even before a patient becomes symptomatic.

Dwg.0/1

L11 ANSWER 31 OF 38 MEDLINE on STN DUPLICATE 6
ACCESSION NUMBER: 2001147256 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11176843
TITLE: **Urine detection** of **survivin** and **diagnosis** of **bladder cancer.**
AUTHOR: Smith S D; Wheeler M A; Plescia J; Colberg J W; Weiss R M; Altieri D C
CORPORATE SOURCE: Yale University School of Medicine, BCMM436B, 295 Congress Ave, New Haven, CT 06536, USA.
CONTRACT NUMBER: CA78810 (NCI)
DK02499 (NIDDK)
DK38311 (NIDDK)
DK47548 (NIDDK)
SOURCE: JAMA : journal of the American Medical Association, (2001 Jan 17) 285 (3) 324-8.
Journal code: 7501160. ISSN: 0098-7484.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010315

AB CONTEXT: Dysregulation of apoptosis may favor onset and progression

of cancer and influence response to therapy. **Survivin** is an inhibitor of apoptosis that is selectively overexpressed in common human cancers, but not in normal tissues, and that correlates with aggressive disease and unfavorable outcomes. OBJECTIVE: To investigate the potential suitability of **survivin detection** in **urine** as a novel predictive/ **prognostic** molecular marker of **bladder cancer**. DESIGN, SETTING, AND PATIENTS: Survey of **urine** specimens from 5 groups: healthy volunteers (n = 17) and patients with nonneoplastic urinary tract disease (n = 30), **genitourinary cancer** (n = 30), new-onset or recurrent **bladder cancer** (n = 46), or treated **bladder cancer** (n = 35), recruited from 2 New England urology clinics. MAIN OUTCOME **MEASURES: Detectable survivin** levels, analyzed by a novel **detection** system and confirmed by Western blot and **reverse transcriptase polymerase chain** reaction (**RT-PCR**), in **urine** samples of the 5 participant groups. RESULTS: **Survivin** was **detected** in the **urine** samples of all 46 patients with new or recurrent **bladder cancer** using a novel **detection** system (31 of 31) and **RT-PCR** (15 of 15) methods. **Survivin** was not **detected** in the **urine** samples of 32 of 35 patients treated for **bladder cancer** and having negative cystoscopy results. None of the healthy volunteers or patients with **prostate, kidney**, vaginal, or cervical **cancer** had **detectable survivin** in **urine** samples. Of the 30 patients with nonneoplastic urinary tract disease, **survivin** was **detected** in 3 patients who had bladder abnormalities noted using cystoscopy and in 1 patient with an increased prostate-specific antigen level. Patients with low-grade **bladder cancer** had significantly lower **urine survivin** levels than patients with **carcinoma** in situ (P =.002). CONCLUSIONS: Highly sensitive and specific **determination** of **urine survivin** appears to provide a simple, noninvasive **diagnostic** test to identify patients with new or recurrent **bladder cancer**.

L11 ANSWER 32 OF 38 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2001:787316 SCISEARCH
THE GENUINE ARTICLE: 475BJ
TITLE: Molecular cloning and characterization of a RING-H2 finger protein, ANAPC11, the human homolog of yeast Apc11p
AUTHOR: Chan A H; Lee S M Y; Chim S S; Kok L D S; Waye M M Y; Lee C Y; Fung K P; Tsui S K W (Reprint)
CORPORATE SOURCE: Chinese Univ Hong Kong, Dept Biochem, Shatin, Hong Kong, Peoples R China (Reprint); Chinese Univ Hong Kong, Hong Kong Bioinformat Ctr, Dept Biochem, Shatin, Hong Kong, Peoples R China
COUNTRY OF AUTHOR: Peoples R China
SOURCE: JOURNAL OF CELLULAR BIOCHEMISTRY, (SEP 2001) Vol. 83, No. 2, pp. 249-258.
Publisher: WILEY-LISS, DIV JOHN WILEY & SONS INC,

605 THIRD AVE, NEW YORK, NY 10158-0012 USA.
ISSN: 0730-2312.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 43

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Yeast Apc11p together with Rbx1 and Roc2/SAG define a new class of RING-H2 fingers in a superfamily of E3 ubiquitin ligases. The human homolog of Apc11p, ANAPC11 was identified during a large-scale partial sequencing of a human liver **cancer** cDNA library and partial characterization was performed. This 514 bp full-length cDNA has a predicted open reading frame (ORF) encoding 84 amino acids. The ORF codes for ANAPC11, the human anaphase promoting complex subunit 11 (yeast APC11 homolog), which possesses a RING-H2 finger motif and exhibits sequence similarity to subunits of E3 ubiquitin ligase complexes. In **Northern blot hybridization** with poly(A) RNA of various human tissues using radio-**labelled** ANAPC11 cDNA probe, we found strong signals **detected** in skeletal muscle and heart; moderate signals **detected** in brain, **kidney**, and liver; and **detectable** but low signals in colon, thymus, spleen, small intestine, placenta, **lung**, and peripheral **blood** leukocyte. The ANAPC11 gene is located at the human chromosome 17q25. ANAPC11 is distributed diffusely in the cytoplasm and nucleus with discrete accumulation in granular structures in all the cell lines (AML 12, HepG2, and C2C12) transfected. Expression level of ANAPC11 is found higher in certain types of **cancer determined** in the RNA **dot blot** experiment. (C) 2001 Wiley-Liss, Inc.

L11 ANSWER 33 OF 38 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2001142722 EMBASE
TITLE: **Survivin**: A new marker for **bladder cancer.**
AUTHOR: Stollerman G.H.
CORPORATE SOURCE: Dr. G.H. Stollerman, 30 Rutgers Road, Wellesley, MA 02481, United States
SOURCE: Hospital Practice, (15 Apr 2001) 36/4 (47-48).
ISSN: 8750-2836 CODEN: HOPRBW
COUNTRY: United States
DOCUMENT TYPE: Journal; Note
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
LANGUAGE: English

L11 ANSWER 34 OF 38 MEDLINE on STN DUPLICATE 7

ACCESSION NUMBER: 2001176877 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11162866
TITLE: Predictive factors in radiotherapy for non-small cell **lung cancer**: present status.
AUTHOR: Choi N; Baumann M; Flentjie M; Kellokumpu-Lehtinen P; Senan S; Zamboglou N; Kosmidis P
CORPORATE SOURCE: Department of Radiation Oncology, Massachusetts General Hospital, Harvard Medical School, Boston, MA 02114, USA.

SOURCE: Lung cancer (Amsterdam, Netherlands), (2001 Jan) 31 (1) 43-56. Ref: 86
Journal code: 8800805. ISSN: 0169-5002.
PUB. COUNTRY: Ireland
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200103
ENTRY DATE: Entered STN: 20010404
Last Updated on STN: 20010404
Entered Medline: 20010329

AB PURPOSE: To evaluate the predictive factors for radiation response in non-small cell **lung cancer** (NSCLC) and the role of such factors in guiding high dose radiation therapy. METHODS: The first International Workshop on **Prognostic** and Predictive Factors in **Lung Cancer** was organized by the Hellenic Cooperative Oncology Group and held in Athens, Greece under the auspices of the International Association for the Study of **Lung Cancer**. Presentations at this meeting provided the outline of this report, which has also been supplemented with available data from the current literature. RESULTS: The predictive factors for both the natural history and the therapy outcome of NSCLC are grouped as follows: (1) tumor related factors (anatomic factors); the extent of tumor (tumor stage) is one of most important **prognostic** factors affecting the therapy outcome. Tumor size (T stage), anatomical structures involved (T4 vs. T3 lesion), and the presence of regional lymph node metastasis have a significant impact on both **prognosis** and response to appropriate therapy; (2) host-related factors (clinical factors) that are important in therapy response include performance status, weight loss of more than 10% of body weight in the previous 6 months, and associated co-morbidities, i.e. pulmonary and cardiac diseases; (3) technical factors of radiation therapy which play a decisive role in successful outcome. The target volume should be defined accurately using modern imaging studies. The radiation dose fractionation schedule, in terms of the dose intensity and total dose, should be high enough to provide local tumor control in the majority of patients. Three-dimensional (3-D) conformal planning is an essential tool in dose escalation studies to **determine** the maximum tolerated dose of radiation; (4) biological/radiobiological/metabolic factors. Biologic markers resulting from genetic lesions in **lung cancer** are grouped as follows: (a) oncogene amplification and overexpression (aberrant gene expression) and mutated **tumor** suppressor genes -- ras gene, myc gene, HER-2/neu and **survivin** gene, p53 and mutated beta-tubulin gene; (b) **tumor** biologic/radiobiologic factors -- **tumor** cell proliferation kinetics, hypoxia, intrinsic cellular radiosensitivity, gamma factor, and DNA content; (c) **enzymes** and hormones: neuron-specific enolase, **serum** lactate dehydrogenase, and enhanced glucose metabolic rate supported by increased glucose transporter protein. The surviving fraction of tumor cells at 2.0 Gy of radiation (SF2) as a **measure** of intrinsic tumor cell radiosensitivity, potential doubling time

(T(Pot)) as a **measure** of the rate of tumor cell proliferation and gamma factor representing the slope of the survival curve at 50% survival rate are being investigated as potential predictors for therapy response. Enhanced glucose utilization, a hallmark of malignant transformation, is being studied as a potential **monitor** for therapy response by using PET-FDG. CONCLUSION: Current data indicate that there is a dose-response relationship between radiation dose and local tumor control, and also between local tumor control and survival in stage III NSCLC. Therapeutic factors, i.e. total radiation dose, fractionation schedule and dose intensity, and use of 3-D conformal radiation to secure the optimum therapeutic ratio are important for improved local tumor control and survival. Future research should be directed towards radiation dose escalation using 3-D conformal therapy to **determine** the maximum tolerated dose (MTD) of radiation in chemo-radiotherapy, and the use of this MTD for improved local tumor control and survival. Radiobiological, molecular, and metabolic markers may have potential for **monitoring** tumor response and optimizing radiation therapy.

L11 ANSWER 35 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2000-687101 [67] WPIDS
CROSS REFERENCE: 2002-471376 [50]
DOC. NO. CPI: C2000-209017
TITLE: Adjuvant composition comprising saponin and immunostimulatory oligonucleotide CpG, useful for producing vaccine formulations for prophylaxis and treatment of cancers, allergy and Alzheimer's disease.
DERWENT CLASS: B04 D16
INVENTOR(S): FRIEDE, M; GARCON, N; HERMAND, P; GERARD, C M G
PATENT ASSIGNEE(S): (SMIK) SMITHKLINE BEECHAM BIOLOGICALS; (SMIK) SMITHKLINE BEECHAN BIOLOGICALS SA
COUNTRY COUNT: 92
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2000062800	A2	20001026	(200067)*	EN	52
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW NL OA PT SD SE SL SZ TZ UG ZW					
W: AE AL AM AT AU AZ BA BB BG BR BY CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG US UZ VN YU ZA ZW					
AU 2000041149	A	20001102	(200107)		
NO 2001005073	A	20011122	(200211)		
BR 2000010612	A	20020213	(200220)		
CZ 2001003774	A3	20020313	(200223)		
EP 1187629	A2	20020320	(200227)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI					
HU 2002000815	A2	20020828	(200264)		
JP 2002542203	W	20021210	(200301)		65
ZA 2001008619	A	20021127	(200305)		70
CN 1372473	A	20021002	(200307)		

KR 2002067617	A	20020823 (200310)
US 6544518	B1	20030408 (200327)
US 2003161834	A1	20030828 (200357)
MX 2001010654	A1	20020301 (200362)
US 6558670	B1	20030506 (200362)
AU 764969	B	20030904 (200368)
NZ 514962	A	20031219 (200404)

APPLICATION DETAILS:

PATENT NO	KIND		APPLICATION	DATE
WO 2000062800	A2		WO 2000-EP2920	20000404
AU 2000041149	A		AU 2000-41149	20000404
NO 2001005073	A		WO 2000-EP2920	20000404
			NO 2001-5073	20011018
BR 2000010612	A		BR 2000-10612	20000404
			WO 2000-EP2920	20000404
CZ 2001003774	A3		WO 2000-EP2920	20000404
			CZ 2001-3774	20000404
EP 1187629	A2		EP 2000-920647	20000404
			WO 2000-EP2920	20000404
HU 2002000815	A2		WO 2000-EP2920	20000404
			HU 2002-815	20000404
JP 2002542203	W		JP 2000-611936	20000404
			WO 2000-EP2920	20000404
ZA 2001008619	A		ZA 2001-8619	20011019
CN 1372473	A		CN 2000-808836	20000404
KR 2002067617	A		KR 2001-713357	20011019
US 6544518	B1	CIP of	US 1999-301829	19990429
		CIP of	WO 2000-EP2920	20000404
			US 2000-690921	20001018
US 2003161834	A1	CIP of	US 1999-301829	19990429
		CIP of	WO 2000-EP2920	20000404
		Div ex	US 2000-690921	20001018
			US 2003-379164	20030303
MX 2001010654	A1		WO 2000-EP2920	20000404
			MX 2001-10654	20011019
US 6558670	B1		US 1999-301829	19990429
AU 764969	B		AU 2000-41149	20000404
NZ 514962	A		NZ 2000-514962	20000404
			WO 2000-EP2920	20000404

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2000041149	A	Based on	WO 2000062800
BR 2000010612	A	Based on	WO 2000062800
CZ 2001003774	A3	Based on	WO 2000062800
EP 1187629	A2	Based on	WO 2000062800
HU 2002000815	A2	Based on	WO 2000062800
JP 2002542203	W	Based on	WO 2000062800
US 2003161834	A1	Div ex	US 6544518
		CIP of	US 6558670
MX 2001010654	A1	Based on	WO 2000062800

Searcher : Shears 571-272-2528

AU 764969	B	Previous Publ.	AU 2000041149
		Based on	WO 2000062800
NZ 514962	A	Based on	WO 2000062800

PRIORITY APPLN. INFO: US 1999-301829 19990429; GB 1999-8885 19990419

AN 2000-687101 [67] WPIDS

CR 2002-471376 [50]

AB WO 200062800 A UPAB: 20040115

NOVELTY - An adjuvant composition (I) comprising a saponin and an immunostimulatory oligonucleotide.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:

(1) a vaccine composition (II) comprising (I) and an antigen;

(2) a delivery device pre-filled with (II) designed to administer the vaccine systemically;

(3) use of a vaccine as a medicament;

(4) use of a combination of saponin and CpG molecule (immunostimulatory oligonucleotides containing unmethylated CpG dinucleotides) in the manufacture of a vaccine for the prophylaxis and treatment of viral, bacterial and parasitic infections, allergy, cancer or other chronic disorders;

(5) making (I) involves admixing a saponin with an immunostimulatory oligonucleotide and optionally a carrier; and

(6) making (II) involves admixing saponin, immunostimulatory oligonucleotide, an antigen and optionally a carrier.

ACTIVITY - Cytostatic; antiallergic; antiatherosclerotic; nootropic; neuroprotective; antibacterial; antiviral; antiparasitic.

MECHANISM OF ACTION - Vaccine. The biological activity of (II) was tested in mice. Female Balb/c mice (5 animals per group), aged 8 weeks, were immunized intramuscularly with lipo-OspA (1 mu g) formulated onto alum (50 mu g). After 3 months, the mice were boosted intranasally with a solution containing 5 mu g lipo-OspA in either A, B, C, D or E.

(A) PBS;

(B) 20 mu g CpG 1001 (TCC ATG AGC TTC CTG ACG TT, Kreig 1826);

(C) 5 micro g QS21;

(D) 20 micro g CpG 1001 + 5 micro g QS21; or

(E) by intramuscular injection of 1 micro g lipo-OspA absorbed onto alum (50 micro g).

OspA-specific **serum** IgG in mice was **measured** by **enzyme** linked immunoabsorbant **assay** (**ELISA**). CpG as well as QS21 significantly improved the intranasal boosting of systemic antibodies to Lipo-OspA. Moreover, when both adjuvants were combined, a synergistic effect of those responses was clearly demonstrated, especially in terms of LA2 antibodies. Humoral responses elicited in the presence of QS21 and CpG were significantly higher than those induced by the parenteral booster.

USE - A vaccine composition containing (I) administered systemically, is useful for inducing an immune response in an individual and for preventing or treating an individual susceptible to or suffering from a disease. Diseases include **prostate, breast, colorectal, lung, pancreatic, renal,** ovarian or melanoma **cancers;** non-**cancer** chronic disorders such as

allergy, Alzheimer and atherosclerosis. The vaccine is useful for prophylaxis and treatment of viral, bacterial and parasitic infections too (claimed).
Dwg.0/12

L11 ANSWER 36 OF 38 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 2000227231 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10766164
TITLE: Antibody response to the tumor-associated inhibitor of apoptosis protein **survivin** in cancer patients.
AUTHOR: Rohayem J; Diestelkoetter P; Weigle B; Oehmichen A; Schmitz M; Mehlhorn J; Conrad K; Rieber E P
CORPORATE SOURCE: Institute for Immunology, Medical Faculty, Technical University of Dresden, Germany.
SOURCE: Cancer research, (2000 Apr 1) 60 (7) 1815-7. Journal code: 2984705R. ISSN: 0008-5472.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200005
ENTRY DATE: Entered STN: 20000512
Last Updated on STN: 20000512
Entered Medline: 20000504

AB Antibody reactivity against **survivin**, a recently identified **tumor**-associated protein, was **determined** in **sera** from patients with **lung** (n = 51) or **colorectal cancer** (n = 49). The same collection of **sera** was tested for the presence of antibodies against p53. Eleven **sera** from **lung cancer** patients and four **sera** from **colorectal cancer** patients reacted with purified recombinant **survivin** in an **ELISA** (21.6% and 8.2%, respectively), whereas four **sera** from **lung cancer** patients and nine **sera** from **colorectal cancer** patients contained anti-p53 antibodies (7.8% and 18.4%, respectively). The increase in prevalence when anti-**survivin** and anti-p53 antibodies were **determined** in parallel was statistically significant (29.4% versus 7.8%, P = 0.005 in **lung cancer** population; 26.6% versus 8.2%, P = 0.015 in **colorectal cancer** population). The high prevalence of anti-**survivin** antibodies makes these antibodies an attractive novel marker for the **diagnosis** of **lung** and **colorectal cancer**, particularly in patients lacking anti-p53 antibodies.

L11 ANSWER 37 OF 38 MEDLINE on STN DUPLICATE 9
ACCESSION NUMBER: 2000162332 MEDLINE
DOCUMENT NUMBER: PubMed ID: 10698506
TITLE: High expression of **Survivin**, mapped to 17q25, is significantly associated with poor **prognostic** factors and promotes cell survival in human **neuroblastoma**.
AUTHOR: Islam A; Kageyama H; Takada N; Kawamoto T; Takayasu

H; Isogai E; Ohira M; Hashizume K; Kobayashi H; Kaneko Y; Nakagawara A

CORPORATE SOURCE: Division of Biochemistry, Chiba Cancer Research Center Research Institute, Japan.

SOURCE: Oncogene, (2000 Feb 3) 19 (5) 617-23. Journal code: 8711562. ISSN: 0950-9232.

PUB. COUNTRY: ENGLAND: United Kingdom

DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 200003

ENTRY DATE: Entered STN: 20000327
Last Updated on STN: 20000327
Entered Medline: 20000316

AB **Survivin** (SVV) is a family member of inhibitor of apoptosis proteins (IAPs) and its expression is cell cycle regulated. The gene is mapped to chromosome 17q25, the region of which is frequently gained in advanced stages of **neuroblastoma** (NBL). However, the role of SVV in NBL is poorly understood. Here we studied the clinical and biological role of SVV in NBL. A 1.9 kb SVV transcript was expressed in all of 9 NBL cell lines at higher levels than those in adult cancer cell lines. In 34 primary NBLs, high levels of SVV expression was significantly associated with age greater than 12 months (two sample t-test: P= 0.0003), advanced stages (P = 0.0136), sporadic tumors (P= 0.0027) and low levels of TrkA expression (P = 0.0030). In NBL cell lines, SVV mRNA expression was dramatically down-regulated in CHP134 and IMR32 cells undergoing apoptosis after treatment with all-trans retinoic acid (RA) or **serum** deprivation. It was only moderately decreased in cells (SH-SY5Y and CHP901) undergoing RA-induced differentiation. On the other hand, in proliferating NBL cells or RA-treated SK-N-AS line which is refractory to RA, the SVV mRNA remained at steady state levels or rather up-regulated. Furthermore, transfection of SVV into CHP134 cells induced remarkable inhibition of the RA-induced apoptosis. Collectively, our results suggest that high expression of SVV is a strong **prognostic** indicator for the advanced stage **neuroblastomas**, and that it could be one of the candidate genes for the 17q gain.

L11 ANSWER 38 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2000:176788 BIOSIS

DOCUMENT NUMBER: PREV200000176788

TITLE: Bcl-2, **survivin** and variant CD44 v7-v10 are downregulated and p53 is upregulated in **breast cancer** cells by progesterone: Inhibition of cell growth and induction of apoptosis.

AUTHOR(S): Formby, B. [Reprint author]; Wiley, T. S.

CORPORATE SOURCE: Sansum Medical Research Institute, 2219 Bath Street, Santa Barbara, CA, 93105, USA

SOURCE: Molecular and Cellular Biochemistry, (Dec., 1999) Vol. 202, No. 1-2, pp. 53-61. print. CODEN: MCBIB8. ISSN: 0300-8177.

DOCUMENT TYPE: Article

LANGUAGE: English
ENTRY DATE: Entered STN: 3 May 2000
Last Updated on STN: 4 Jan 2002

AB Progesterone inhibits the proliferation of normal **breast** epithelial cells in vivo, as well as **breast cancer** cells in vitro. But the biologic mechanism of this inhibition remains to be **determined**. We explored the possibility that an antiproliferative activity of progesterone in **breast cancer** cell lines is due to its ability to induce apoptosis. Since p53, bcl-2 and **survivin** genetically control the apoptotic process, we investigated whether or not these genes could be involved in the progesterone-induced apoptosis. We found a maximal 90% inhibition of cell proliferation with T47-D **breast cancer** cells after exposure to 10 muM progesterone for 72 h. Control progesterone receptor negative MDA-231 cancer cells were unresponsive to 10 muM progesterone. The earliest sign of apoptosis is translocation of phosphatidylserine from the inner to the outer leaflet of the **plasma** membrane and can be **monitored** by the calcium-dependent binding of annexin V in conjunction with flow cytometry. After 24 h of exposure to 10 muM progesterone, cytofluorometric analysis of T47-D **breast cancer** cells indicated 43% were annexin V-positive and had undergone apoptosis and no cells showed signs of cellular necrosis (propidium iodine negative). After 72 h of exposure to 10 muM progesterone, 48% of the cells had undergone apoptosis and 40% were annexin V positive/propidium iodide positive indicating signs of necrosis. Control untreated cancer cells did not undergo apoptosis. Evidence proving apoptosis was also demonstrated by fragmentation of nuclear DNA into multiples of oligonucleosomal fragments. After 24 h of exposure of T47-D cells to either 1 or 10 muM progesterone, we observed a marked down-regulation of protooncogene bcl-2 protein and mRNA levels. mRNA levels of **survivin** and the metastatic variant CD44 v7-v10 were also downregulated. Progesterone increased p53 mRNA levels. These results demonstrate that progesterone at relative high physiological concentrations, but comparable to those seen in **plasma** during the third trimester of human pregnancy, exhibited a strong antiproliferative effect on **breast cancer** cells and induced apoptosis.

FILE 'HCAPLUS, MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 12:40:12 ON 22 JUN 2004

L12	717	SEA ABB=ON	PLU=ON	"ALTIERI D"?/AU
L13	14691	SEA ABB=ON	PLU=ON	"WEISS R"?/AU
L14	43859	SEA ABB=ON	PLU=ON	"SMITH S"?/AU
L15	2173	SEA ABB=ON	PLU=ON	"MORRIS V"?/AU
L16	4404	SEA ABB=ON	PLU=ON	"WHEELER M"?/AU
L17	222	SEA ABB=ON	PLU=ON	"PLESCIA J"?/AU
L18	1	SEA ABB=ON	PLU=ON	L12 AND L13 AND L14 AND L15 AND L16 AND L17
L19	158	SEA ABB=ON	PLU=ON	L12 AND (L13 OR L14 OR L15 OR L16 OR L17)
L20	307	SEA ABB=ON	PLU=ON	L13 AND (L14 OR L15 OR L16 OR L17)
L21	121	SEA ABB=ON	PLU=ON	L14 AND (L15 OR L16 OR L17)
L22	1	SEA ABB=ON	PLU=ON	L15 AND (L16 OR L17)
L23	8	SEA ABB=ON	PLU=ON	L16 AND L17

- Author (s)

Searcher : Shears 571-272-2528

L24 43 SEA ABB=ON PLU=ON (L19 OR L20 OR L21 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17) AND L5
L25 43 SEA ABB=ON PLU=ON L18 OR L22 OR L23 OR L24
L26 15 DUP REM L25 (28 DUPLICATES REMOVED)

L26 ANSWER 1 OF 15 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:1039904 SCISEARCH
THE GENUINE ARTICLE: 745YX
TITLE: **Survivin**, versatile modulation of cell division and apoptosis in cancer
AUTHOR: **Altieri D C (Reprint)**
CORPORATE SOURCE: Univ Massachusetts, Sch Med, Dept Canc Biol, 364 Plantat St, Worcester, MA 01605 USA (Reprint); Univ Massachusetts, Sch Med, Dept Canc Biol, Worcester, MA 01605 USA; Univ Massachusetts, Sch Med, Ctr Canc, Worcester, MA 01605 USA
COUNTRY OF AUTHOR: USA
SOURCE: ONCOGENE, (24 NOV 2003) Vol. 22, No. 53, pp. 8581-8589.
Publisher: NATURE PUBLISHING GROUP, MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND.
ISSN: 0950-9232.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 132

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Survivin** is a member of the inhibitor of apoptosis (IAP) gene family that has attracted attention from several viewpoints of basic and translational research. Its cell cycle-regulated expression at mitosis and association with the mitotic apparatus have been of interest to cell biologists studying faithful segregation of sister chromatids and timely separation of daughter cells. Investigators interested in mechanisms of apoptosis have found **survivin** an evolving challenge: while **survivin** inhibits apoptosis in vitro and in vivo, this pathway may be more selective as compared to cytoprotection mediated by other IAPs. Finally, basic and translational researchers in cancer biology have converged on **survivin** as a pivotal cancer gene, not simply for its sharp expression in tumors and not in normal tissues, but also for the potential exploitation of this pathway in cancer **diagnosis** and therapy. The objective of the present contribution is to line up current evidence and emerging concepts on the multifaceted functions of **survivin** in cell death and cell division, and how this pathway is being pursued for novel cancer therapeutic strategies.

L26 ANSWER 2 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 1
ACCESSION NUMBER: 2003:528816 HCAPLUS
DOCUMENT NUMBER: 139:274718
TITLE: Therapeutic Targeting of the **Survivin** Pathway in Cancer: Initiation of Mitochondrial Apoptosis and Suppression of Tumor-associated Angiogenesis
AUTHOR(S): Blanc-Brude, Olivier P.; Mesri, Mehdi; Wall, Nathan R.; **Plescia, Janet**; Dohi, Takehiko; **Altieri, Dario C.**

CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, MA, 01605, USA
SOURCE: Clinical Cancer Research (2003), 9(7), 2683-2692
CODEN: CCREF4; ISSN: 1078-0432
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB PURPOSE: Mol. antagonists of the inhibitor of apoptosis protein **survivin** have shown promise as novel anticancer strategies for triggering tumor cell apoptosis, dysregulating mitotic progression, and inhibiting tumor growth in preclin. models. However, how **survivin** couples to the cell death machinery has remained elusive, and the relevant cellular targets of **survivin** antagonists have not been completely elucidated. Exptl. Design: Human umbilical vein and dermal microvascular endothelial cells were infected with replication-deficient adenoviruses encoding **survivin** (pAd-**Survivin**), green fluorescent protein (pAd-GFP), or a phosphorylation-defective **survivin** Thr34 Ala (pAd-T34A) dominant neg. mutant. The effect of wild-type or mutant **survivin** was investigated on capillary network stability, endothelial cell viability, and caspase activation in vitro and on kinetics of **tumor** growth and development of angiogenesis in a **breast cancer** xenograft model in vivo. The cell death pathway initiated by **survivin** targeting was mapped with respect to cytochrome c release, changes in mitochondrial transmembrane potential, and apoptosome requirements using mouse embryonic fibroblasts deficient in Apaf-1 or caspase-9. RESULTS: Adenoviral transduction of endothelial cells with pAd-**Survivin** inhibited growth factor deprivation- or ceramide-induced apoptosis, reduced caspase-3 and -7 generation, and stabilized three-dimensional capillary networks in vitro. Conversely, expression of pAd-T34A caused apoptosis in umbilical vein and dermal microvascular endothelial cells and resulted in caspase-3 activity. Cell death induced by **survivin** targeting exhibited the hallmarks of mitochondrial-dependent apoptosis with release of cytochrome c and loss of mitochondrial transmembrane potential and was suppressed in Apaf-1 or caspase-9 knockout mouse embryonic fibroblasts. When injected in human **breast cancer** xenografts, pAd-T34A inhibited growth of established **tumors** and triggered **tumor** cell apoptosis in vivo. This was associated with a .apprx.60% reduction in tumor-derived blood vessels by **quant.** morphometry of CD31-stained tumor areas, and appearance of endothelial cell apoptosis by internucleosomal DNA fragmentation in vivo. CONCLUSIONS: **Survivin** functions as a novel upstream regulator of mitochondrial-dependent apoptosis, and mol. targeting of this pathway results in anticancer activity via a dual mechanism of induction of tumor cell apoptosis and suppression of angiogenesis.

REFERENCE COUNT: 43 THERE ARE 43 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 3 OF 15 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003286478 MEDLINE

DOCUMENT NUMBER: PubMed ID: 12796695
TITLE: Effect of intravesical treatment of transitional cell carcinoma with bacillus Calmette-Guerin and mitomycin C on urinary **survivin** levels and outcome.
AUTHOR: Hausladen Derek A; **Wheeler Marcia A**; **Altieri Dario C**; Colberg John W; **Weiss Robert M**
CORPORATE SOURCE: Department of Surgery, Section of Urology, Yale University School of Medicine, PO Box 208041 YPB-3, New Haven, CT 06520-8041, USA.
CONTRACT NUMBER: DK 38311 (NIDDK)
DK 47548 (NIDDK)
SOURCE: Journal of urology, (2003 Jul) 170 (1) 230-4.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030620
Last Updated on STN: 20030710
Entered Medline: 20030709

AB PURPOSE: Urine **survivin** is a predictive/**prognostic** molecular marker that **detects** transitional cell carcinoma (TCC) with high specificity and sensitivity. The presence of urine **survivin** in patients with TCC who receive intravesical instillation of bacillus Calmette-Guerin or mitomycin C may predict recurrence. MATERIALS AND METHODS: Urine from 25 subjects receiving 27 intravesical treatments of bacillus Calmette-Guerin or mitomycin C for TCC were collected prior to, during and after treatment. Urinary **survivin** levels were compared with outcome, as assessed by cytology and cystoscopy with or without biopsy 1 month and up to 12 months after the completion of treatment. RESULTS: Pretreatment **survivin** levels were higher in subjects in whom TCC recurred following treatment compared with those who achieved remission. **Survivin** levels increased several-fold during treatment with the highest **survivin** levels **measured** in subjects with recurrence. Median posttreatment values of **survivin** were zero in those who achieved remission and 1.0 ng/ml urine in subjects in whom TCC recurred. CONCLUSIONS: The presence of urinary **survivin** 1 month after the completion of treatment predicts TCC recurrence with 100% sensitivity and 78% specificity. Specificity to predict TCC recurrence increases to 92% after 1 year. No TCC recurred for 1 year in 12 of the 14 subjects with a posttreatment **survivin** level of 0.1 ng or less per ml urine. Three of the 4 subjects who were **survivin** positive but in remission 1 month after the completion of treatment had recurrent TCC within 1 year. Subjects who have urinary **survivin** after the completion of intravesical instillation have a high likelihood of TCC recurrence.

L26 ANSWER 4 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 3
ACCESSION NUMBER: 2003:564068 HCAPLUS
DOCUMENT NUMBER: 139:289993
TITLE: **Survivin** and molecular pathogenesis of **colorectal cancer**

AUTHOR(S): Kim, Paul J.; **Plescia, Janet**; Clevers, Hans; Fearon, Eric R.; **Altieri, Dario C.**
CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, MA, USA
SOURCE: Lancet (2003), 362(9379), 205-209
CODEN: LANCAO; ISSN: 0140-6736
PUBLISHER: Elsevier Science Ltd.
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Background: **Colorectal cancer** is thought to originate in the expansion of colonic crypt cells as a result of aberrant gene expression caused by transcription factors of the T-cell factor (TCF)/β-catenin family. **Survivin** is a bifunctional regulator of cell death and cell proliferation expressed during embryonic development but undetectable in healthy adult tissues and re-expressed in many **cancers**, including **colorectal cancer**. Methods: The authors investigated gene expression by promoter anal., mutagenesis, and electrophoretic mobility shift assay in **colorectal cancer** cells. **Survivin** expression in human and mouse embryonic intestine was **determined** by in-situ hybridization and immunohistochem. Changes in apoptosis were **monitored** in cell lines engineered to express stabilizing mutations in β catenin. Findings: TCF/β catenin stimulated a 6-fold to 12-fold increased expression of the **survivin** gene in **colorectal cancer** cells. Three TCF-binding elements (TBE) in the **survivin** promoter were occupied by nuclear factors in **colorectal cancer** cells, and mutagenesis of the 2 proximal TBE sites abolished **survivin** gene expression by 75-79%. Strongly expressed at the bottom of human and mouse embryonic intestinal crypts, expression of **survivin** was lost in TCF-4 knockout animals, and a TCF-4 dominant neg. mutant blocked **survivin** gene transcription in **colorectal cancer** cells. Expression of non-destructible β catenin mutants increased **survivin** expression and protected against UV-B-induced apoptosis. Interpretation: Stimulation of **survivin** expression by TCF/β catenin might impose a stem cell-like phenotype to colonic crypt epithelium coupling enhanced cell proliferation with resistance to apoptosis, and contribute to the mol. pathogenesis of **colorectal cancer**.
REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 5 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 4
ACCESSION NUMBER: 2002:555762 HCAPLUS
DOCUMENT NUMBER: 137:121595
TITLE: **Detection** of **survivin** in the biological fluids of cancer patients
INVENTOR(S): **Altieri, Dario C.; Weiss, Robert M.; Smith, Shannon D.; Wheeler, Marcia A.; Plescia, Janet**
PATENT ASSIGNEE(S): Yale University, USA

SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002057787	A2	20020725	WO 2002-US574	20020111
WO 2002057787	A3	20021219		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002160395	A1	20021031	US 2002-42302	20020111
EP 1350114	A2	20031008	EP 2002-714720	20020111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR				

PRIORITY APPLN. INFO.: US 2001-260898P P 20010112
WO 2002-US574 W 20020111

AB The present invention includes a method for **diagnosing** cancer comprising **detecting** the presence of **survivin** in the biol. fluid of a patient. The present invention also provides kits comprising one or more agents that **detect survivin** polypeptide or **survivin** nucleic acid and a container for collecting biol. fluid for testing.

L26 ANSWER 6 OF 15 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 5

ACCESSION NUMBER: 2002:444088 BIOSIS
DOCUMENT NUMBER: PREV200200444088
TITLE: Urinary **survivin** testing to **monitor bladder cancer** burden in patients receiving intravesical chemotherapy.
AUTHOR(S): Hausladen, Derek A. [Reprint author]; **Wheeler, Marcia A.** [Reprint author]; Colberg, John W. [Reprint author]; **Altieri, Dario C.** [Reprint author]; **Weiss, Robert M.** [Reprint author]
CORPORATE SOURCE: New Haven, CT, USA
SOURCE: Journal of Urology, (April, 2002) Vol. 167, No. 4 Supplement, pp. 162. print.
Meeting Info.: Annual Meeting of the American Urology Association, Inc. Orlando, Florida, USA. May 25-30, 2002.
CODEN: JOURAA. ISSN: 0022-5347.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 21 Aug 2002
Last Updated on STN: 21 Aug 2002

L26 ANSWER 7 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 6
ACCESSION NUMBER: 2002:229863 HCAPLUS
DOCUMENT NUMBER: 137:138159
TITLE: **Bladder cancer detection** with urinary **survivin**, an inhibitor of apoptosis
AUTHOR(S): Sharp, Jennifer D.; Hausladen, Derek A.; Maher, M. Grey; **Wheeler, Marcia A.**; Altieri, C.; **Weiss, Robert M.**
CORPORATE SOURCE: Department of Surgery (Section of Urology) and Pathology (Boyer Center for Molecular Medicine), Yale University School of Medicine, New Haven, CT, USA
SOURCE: Frontiers in Bioscience [online computer file] (2002), 7, E36-E41
CODEN: FRBIF6; ISSN: 1093-4715
URL: http://www.bioscience.org/2002/v7/e/sharp/pdf.pdf
PUBLISHER: Frontiers in Bioscience
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English
AB A review. The current "gold standard" for the **diagnosis** of **bladder cancer** is cystoscopy and urine cytol. Cystoscopy, a naked eye assessment of the bladder, is invasive, uncomfortable and costly while cytol. has high specificity but low sensitivity (40-60%) particularly for low-grade lesions. Therefore, there is a need for a mol. tumor marker assay that is simple to perform and sensitive, particularly for low-grade lesions. By looking to the pathophysiol. of **bladder cancer**, we identified **survivin**, an inhibitor of apoptosis that is not generally expressed in fully differential adult tissue and is highly expressed in **bladder cancer**. **Survivin** is **detected** in whole urine of patients with TCC using a simple antibody based test. The sensitivity of **survivin** testing for new or recurrent **bladder cancer** is 100% while the specificity for other **neoplastic** and non-**neoplastic genitourinary** disease is 95%. The high sensitivity of this simple, noninvasive test is well suited to **bladder cancer**, a disease with high rates of recurrence.
REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 8 OF 15 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2001:999249 SCISEARCH
THE GENUINE ARTICLE: 500FP
TITLE: The molecular basis and potential role of **survivin** in cancer **diagnosis** and therapy
AUTHOR: **Altieri D C (Reprint)**
CORPORATE SOURCE: Yale Univ, Sch Med, Boyer Ctr Mol Med, Dept Pathol,

295 Congress Ave, New Haven, CT 06536 USA (Reprint); Yale Univ, Sch Med, Boyer Ctr Mol Med, Dept Pathol, New Haven, CT 06536 USA
COUNTRY OF AUTHOR: USA
SOURCE: TRENDS IN MOLECULAR MEDICINE, (DEC 2001) Vol. 7, No. 12, pp. 542-547.
Publisher: ELSEVIER SCI LTD, THE BOULEVARD, LANGFORD LANE, KIDLINGTON, OXFORD OX5 1GB, OXON, ENGLAND.
ISSN: 1471-4914.
DOCUMENT TYPE: General Review; Journal
LANGUAGE: English
REFERENCE COUNT: 66
ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Despite its genetic complexity and multifactoriality, two processes appear almost universally compromised in cancer: the control of cell proliferation and the regulation of cell lifespan. **Survivin** is a recently described molecule that has been implicated in both processes, and is overexpressed in most human cancers. The exploitation of the **survivin** signaling pathway might provide important predictive and **prognostic** clues in cancer **diagnosis**, and offer new therapeutic alternatives for cancer treatment.

L26 ANSWER 9 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 7
ACCESSION NUMBER: 2001:65575 HCAPLUS
DOCUMENT NUMBER: 135:31997
TITLE: Urine **detection** of **survivin** and **diagnosis** of **bladder cancer**
AUTHOR(S): **Smith, Shannon D.; Wheeler, Marcia A.; Plescia, Janet;** Colberg, John W.; **Weiss, Robert M.; Altieri, Dario C.**
CORPORATE SOURCE: Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, 06536, USA
SOURCE: JAMA, the Journal of the American Medical Association (2001), 285(3), 324-328
CODEN: JAMAAP; ISSN: 0098-7484
PUBLISHER: American Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Context Dysregulation of apoptosis may favor onset and progression of cancer and influence response to therapy. **Survivin** is an inhibitor of apoptosis that is selectively overexpressed in common human cancers, but not in normal tissues, and that correlates with aggressive disease and unfavorable outcomes. Objective To investigate the potential suitability of **survivin** **detection** in urine as a novel predictive/**prognostic** mol. marker of **bladder cancer**. Design, Setting, and Patients Survey of urine specimens from 5 groups: healthy volunteers (n=17) and patients with nonneoplastic urinary tract disease (n=30), **genitourinary cancer** (n=30), new-onset or recurrent **bladder cancer** (n=46), or treated **bladder cancer** (n=35), recruited from 2 New England urol. clinics. Main Outcome **Measures**

Detectable survivin levels, analyzed by a novel **detection** system and confirmed by Western blot and reverse transcriptase polymerase chain reaction (RT-PCR), in urine samples of the 5 participant groups. Results **Survivin** was **detected** in the urine samples of all 46 patients with new or recurrent **bladder cancer** using a novel **detection** system (31 of 31) and RT-PCR (15 of 15) methods. **Survivin** was not **detected** in the urine samples of 32 of 35 patients treated for **bladder cancer** and having neg. cystoscopy results. None of the healthy volunteers or patients with **prostate, kidney**, vaginal, or cervical **cancer** had **detectable survivin** in urine samples. Of the 30 patients with nonneoplastic urinary tract disease, **survivin** was **detected** in 3 patients who had bladder abnormalities noted using cystoscopy and in 1 patient with an increased prostate-specific antigen level. Patients with low-grade **bladder cancer** had significantly lower urine **survivin** levels than patients with **carcinoma** in situ (P=.002). Conclusions Highly sensitive and specific **determination** of urine **survivin** appears to provide a simple, noninvasive **diagnostic** test to identify patients with new or recurrent **bladder cancer.**

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 10 OF 15 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2001:305697 BIOSIS
DOCUMENT NUMBER: PREV200100305697
TITLE: Expression and **prognostic** significance of **survivin** in de novo acute myeloid leukemia (AML).
AUTHOR(S): Adida, C. [Reprint author]; Recher, C.; Raffoux, E.; Daniel, M. T.; Taksin, A. L.; Rousselot, P.; Sigaux, F.; Degos, L.; **Altieri, D. C.** [Reprint author]; Dombret, H.
CORPORATE SOURCE: Yale University School of Medicine, New Haven, USA
SOURCE: Blood, (November 16, 2000) Vol. 96, No. 11 Part 1, pp. 698a. print.
Meeting Info.: 42nd Annual Meeting of the American Society of Hematology. San Francisco, California, USA. December 01-05, 2000. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
Conference; (Meeting Poster)
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Jun 2001
Last Updated on STN: 19 Feb 2002

AB **Survivin** is an inhibitor of apoptosis over-expressed in various human **cancers** including **neuroblastoma**, non-Hodgkin lymphoma, and **colorectal** or **bladder cancers**, but undetectable in normal differentiated tissues.

A potential distribution and **prognostic** significance of **survivin** in 125 patients with de novo acute myeloid leukemia (AML) was investigated. By immunofluorescence of bone marrow specimens and peripheral blood mononuclear cells, **survivin** was **detected** in 75 out of 125 AML cases (60%), with reactivity in 50-90% of AML cells in almost all positive cases. **Survivin** expression correlated with lower WBC (P=0.008 by the Mann-Whitney test) and was associated in the 55 cases FAB-M0-M1-M2 with leukemic granulocytic maturation (1/5 M0, 11/22 M1, and 23/28 M2; P=0.007 by the Fisher test). In 69 patients treated with the ALFA 9000 protocol, **survivin** expression was significantly associated with lower WBC (P=0.03 by the Mann-Whitney test) and non-unfavorable cytogenetics (P=0.03 by the Fisher test). There was no significant difference in complete remission (CR) rate between **survivin**-positive and **survivin**-negative patients (76% versus 80%). With a median follow-up of 4.6 years, the risk of AML relapse was similar in both patient groups, but there was a trend for earlier relapses in **survivin**-positive patients when compared to **survivin** -negative patients (estimated 1-year relapse rate, 38% versus 19%; median CR duration, 17 versus 31 months). When tested in univariate analysis, **survivin** expression did not significantly influence overall survival (P=0.15 by the log-rank test). However, **survivin** expression became an independent negative **prognostic** factor for survival when adjusted with the Cox model for established **prognostic** factors in AML (cytogenetics, age, and WBC) and for ALFA 9000 treatment arm (RR=2.8 and P=0.03, by the likelihood-ratio test). These data suggest that **survivin** expression may be considered as a new unfavorable **prognostic** factor of de novo AML, and suggest a role of apoptosis inhibition in influencing disease outcome.

L26 ANSWER 11 OF 15 MEDLINE on STN DUPLICATE 8
ACCESSION NUMBER: 1998184286 MEDLINE
DOCUMENT NUMBER: PubMed ID: 9525374
TITLE: Anti-apoptosis gene, **survivin**, and **prognosis** of **neuroblastoma**.
AUTHOR: Adida C; Berrebi D; Peuchmaur M; Reyes-Mugica M; **Altieri D C**
CONTRACT NUMBER: HL-54131 (NHLBI)
RO1 HL-43773 (NHLBI)
SOURCE: Lancet, (1998 Mar 21) 351 (9106) 882-3.
Journal code: 2985213R. ISSN: 0140-6736.
PUB. COUNTRY: ENGLAND: United Kingdom
DOCUMENT TYPE: Letter
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 199804
ENTRY DATE: Entered STN: 19980422
Last Updated on STN: 19980422
Entered Medline: 19980410

L26 ANSWER 12 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 1998:352941 HCAPLUS
DOCUMENT NUMBER: 129:52672
TITLE: **Survivin**: a protein that inhibits

cellular apoptosis, the gene encoding it and the development of modulators of protein activity

INVENTOR(S): **Altieri, Dario C.**
PATENT ASSIGNEE(S): Yale University, USA; Altieri, Dario C.
SOURCE: PCT Int. Appl., 109 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9822589	A2	19980528	WO 1997-US21880	19971120
WO 9822589	A3	19981029		
W: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, KE, LS, MW, SD, SZ, UG, ZW, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
AU 9873018	A1	19980610	AU 1998-73018	19971120
AU 736587	B2	20010802		
EP 950103	A2	19991020	EP 1997-949685	19971120
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
US 6245523	B1	20010612	US 1997-975080	19971120
JP 2002514060	T2	20020514	JP 1998-524007	19971120
KR 2000057159	A	20000915	KR 1999-704445	19990520
US 2003100525	A1	20030529	US 2002-138618	20020506

PRIORITY APPLN. INFO.:
US 1996-31435P P 19961120
US 1997-975080 A 19971120
WO 1997-US21880 W 19971120
US 2000-690825 A3 20001018

AB A novel apoptosis-regulating protein termed "**Survivin**" is identified and a cDNA encoding it is cloned. The protein inhibits apoptosis and may be a target for the treatment of proliferative diseases such as cancers (no data) and as a tool for investigating apoptosis in normal and diseased states. The protein is abundant in tumor cells but is present at low levels in normal, terminally differentiated adult cells but is **detectable** in many fetal tissues. Aggressive tumors showed the highest levels of **survivins** and **survivin** levels may be a **prognostic** indicator for some tumors. Amino acid residues essential for protein function were identified by alanine scanning mutagenesis. The cloned human gene was found to include a gene on the antisense strand that encoded a protein with features typical of an apoptosis-inhibiting protein.

L26 ANSWER 13 OF 15 HCAPLUS COPYRIGHT 2004 ACS on STN DUPLICATE 9
ACCESSION NUMBER: 1998:750551 HCAPLUS
DOCUMENT NUMBER: 130:108444
TITLE: Inhibition of apoptosis by **survivin**

predicts shorter survival rates in **colorectal cancer**

AUTHOR(S): Kawasaki, Hiroshi; **Altieri, Dario C.**; Lu, Cai-De; Toyoda, Masao; Tenjo, Toshiyuki; Tanigawa, Nobuhiko

CORPORATE SOURCE: Department of General and Gastroenterological Surgery, Osaka Medical College, Takatsuki City, 569-8686, Japan

SOURCE: Cancer Research (1998), 58(22), 5071-5074
CODEN: CNREA8; ISSN: 0008-5472

PUBLISHER: AACR Subscription Office

DOCUMENT TYPE: Journal

LANGUAGE: English

AB Deregulated inhibition of apoptosis (programmed cell death) may facilitate the insurgence of neoplasia, but whether it also influences the outcome of common cancers has remained controversial. In this study, the authors investigated the expression of a novel inhibitor of apoptosis, **survivin**, in **colorectal cancer** and its relation with **tumor** cell apoptosis and overall **prognosis**. By immunohistochem., **survivin** was expressed in 91 of 171 (53.2%) cases of **colorectal carcinomas** of histol. stages 0 to IV. In contrast, normal colon epithelium did not express **survivin**. Although **survivin** expression did not correlate with p53 abnormalities (46.5% vs. 58.0%), **survivin** -pos. cases were strongly associated with bcl-2 expression (72.5% vs. 27.4%) and reduced apoptotic index (0.76% vs. 1.17%). Expression of **survivin** alone in bcl-2-neg. (discordant) cases also resulted in reduced apoptotic index (0.82% vs. 1.16%). When analyzed for **prognostic** significance, patients with low apoptotic index (<0.97%) had worse survival rates than the group with high apoptosis, and a multivariate Cox proportional hazard model identified reduced apoptosis as an independent predictive factor for overall survival. These data demonstrate that apoptosis inhibition by **survivin**, alone or in cooperation with bcl-2, is an important predictive/**prognostic** parameter of poor outcome in **colorectal carcinoma** and identify **survivin** as a new **diagnostic** /therapeutic target in **cancer**.

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L26 ANSWER 14 OF 15 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN DUPLICATE 10

ACCESSION NUMBER: 1998:365594 BIOSIS
DOCUMENT NUMBER: PREV199800365594

TITLE: Anti-apoptosis gene, surviving and **prognosis** of **neuroblastoma**.

AUTHOR(S): Adida, Colette [Reprint author]; Berrebi, Dominique; Peuchmaur, Michael; Reyes-Mugica, Miguel; **Altieri, Dario C.**

CORPORATE SOURCE: Dep. Pathol., Boyer Cent. Mol. Med., Yale Univ. Sch. Med., 295 Congress Ave., New Haven, CT 06536, USA

SOURCE: Lancet (North American Edition), (March 21, 1998) Vol. 351, No. 9106, pp. 882-883. print.

ISSN: 0099-5355.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 27 Aug 1998
Last Updated on STN: 27 Aug 1998

L26 ANSWER 15 OF 15 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 1998:235309 SCISEARCH
THE GENUINE ARTICLE: ZD047
TITLE: Anti-apoptosis gene, **survivin**, and **prognosis** of **neuroblastoma**
AUTHOR: Adida C (Reprint); Berrebi D; Peuchmaur M; ReyesMugica M; **Altieri D C**
CORPORATE SOURCE: YALE UNIV, SCH MED, BOYER CTR MOL MED, DEPT PATHOL, 295 CONGRESS AVE, NEW HAVEN, CT 06536 (Reprint); YALE UNIV, SCH MED, BOYER CTR MOL MED, DEPT PAEDIAT, NEW HAVEN, CT 06536; HOP ROBERT DEBRE, DEPT PATHOL, F-75019 PARIS, FRANCE
COUNTRY OF AUTHOR: USA; FRANCE
SOURCE: LANCET, (21 MAR 1998) Vol. 351, No. 9106, pp. 882-883.
Publisher: LANCET LTD, 42 BEDFORD SQUARE, LONDON, ENGLAND WC1B 3SL.
ISSN: 0140-6736.
DOCUMENT TYPE: Article; Journal
FILE SEGMENT: LIFE; CLIN
LANGUAGE: English
REFERENCE COUNT: 5

FILE 'HOME' ENTERED AT 12:47:05 ON 22 JUN 2004

Harris, A.
10/042302

FILE 'REGISTRY' ENTERED AT 12:16:09 ON 22 JUN 2004
E SURVIVIN/CN

-key terms

L1 17 SEA ABB=ON PLU=ON (SURVIVIN/CN OR "SURVIVIN (10-ALANINE)(HUMAN)"/CN OR "SURVIVIN (10-ALANINE,93-ALANINE,98-ARGININE)(HUMAN)"/CN OR "SURVIVIN (10-ALANINE,98-ALANINE,101-ARGININE,102-SERINE)(HUMAN)"/CN OR "SURVIVIN (34-GLUTAMIC ACID)(HUMAN)"/CN OR "SURVIVIN (54-METHIONINE)(HUMAN)"/CN OR "SURVIVIN (6-GLYCINE,10-ALANINE,98-ALANINE,101-ARGININE,102-SERINE)(HUMAN)"/CN OR "SURVIVIN (6-GLYCINE,10-ALANINE93-ALANINE98-ARGININE)(HUMAN)"/CN OR "SURVIVIN (76-ALANINE,80-ALANINE)(HUMAN)"/CN OR "SURVIVIN (80-ALANINE)(HUMAN)"/CN OR "SURVIVIN (97-GLUTAMIC ACID)(HUMAN)"/CN OR "SURVIVIN (CHICKEN Δ ISOFORM)"/CN OR "SURVIVIN (CHICKEN Γ ISOFORM)"/CN OR "SURVIVIN (CHICKEN SHORT ISOFORM)"/CN OR "SURVIVIN (CHICKEN)"/CN OR "SURVIVIN (HUMAN GENE SURVIVIN)"/CN OR "SURVIVIN (HUMAN)"/CN OR "SURVIVIN (XENOPUS LAEVIS)"/CN)

FILE 'HCAPLUS' ENTERED AT 12:16:21 ON 22 JUN 2004

L2 624 SEA ABB=ON PLU=ON L1 OR SURVIVIN

L3 135639 SEA ABB=ON PLU=ON (GENITOURINARY OR BLADDER OR PROSTAT? OR UROGENITAL OR URO GENITAL OR GENITO URINARY OR KIDNEY OR RENAL OR PANCREAS OR PANCREAT? OR COLORECTAL OR (COLO OR COLON)(3A)RECTAL OR BREAST OR LUNG OR BLADDER)(S)(CANCER? OR CARCIN? OR TUMOUR OR TUMOR OR NEOPLAS?)

L4 173 SEA ABB=ON PLU=ON L2 AND (L3 OR NEUROBLASTOM? OR NEURO BLASTOM? OR MAMMAR?(S)(CANCER? OR CARCIN? OR NEOPLAS? OR TUMOUR OR TUMOR))

L5 121 SEA ABB=ON PLU=ON L4 AND (DIAGNOS? OR DETERM? OR DETECT? OR DET## OR SCREEN? OR MONITOR? OR PROGNOS? OR MEAS? OR QUANT?)

L6 34 SEA ABB=ON PLU=ON L5 AND (URINE OR SERUM OR SERA OR BLOOD OR PLASMA OR (PROSTAT? OR SEMINAL OR BREAST OR MAMMAR? OR VAGINA? OR GI(S)(GASTROINTEST? OR GASTRO INTESTIN?) OR GASTROINTESTIN? OR GASTRO INTESTIN?)(S)FLUID)

L7 19 SEA ABB=ON PLU=ON L6 AND (LABEL? OR ENZYME OR IMMUNOASSAY? OR ASSAY? OR RADIOIMMUNOASSAY? OR ELISA OR IMMUNOBLOT? OR IMMUNODIFFUS? OR IMMUNOELECTROPHOR? OR IMMUNOPRECIPITAT? OR IMMUNO?(W)(BLOT? OR DIFFUS? OR ELECTROPHOR? OR PRECIPITAT?) OR DOT BLOT? OR BIODOT OR BIO DOT OR HYBRIDIS? OR HYBRIDIZ?)

L8 5 SEA ABB=ON PLU=ON L6 AND ((CHEMILUMINESC? OR CHEMILUMINESC?)(3A)(TAG OR TAGGING OR TAGGED) OR (RT OR REVERS? TRANSCRIPT?)(W)(PCR OR POLYMERASE CHAIN) OR NORTHERN BLOT?)

L9 21 SEA ABB=ON PLU=ON L7 OR L8

L9 ANSWER 1 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Jun 2004
ACCESSION NUMBER: 2004:449884 HCAPLUS
DOCUMENT NUMBER: 140:420388
TITLE: Binary prediction tree modeling with many predictors and its uses in clinical and genomic applications

Searcher : Shears 571-272-2528

INVENTOR(S): Nevins, Joseph R.; West, Mike; Huang, Andrew T.
PATENT ASSIGNEE(S): Duke University, USA
SOURCE: PCT Int. Appl., 886 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 5
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004038376	A2	20040506	WO 2003-XB33946	20031024

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

WO 2004038376	A2	20040506	WO 2003-US33946	20031024

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.:

US 2002-420729P	P	20021024
US 2002-421062P	P	20021025
US 2002-421102P	P	20021025
US 2002-424701P	P	20021108
US 2002-424715P	P	20021108
US 2002-424718P	P	20021108
US 2002-425256P	P	20021112
US 2003-448461P	P	20030221
US 2003-448462P	P	20030221
US 2003-457877P	P	20030327
US 2003-458373P	P	20030331
WO 2003-US33946	A	20031024

AB The statistical anal. described and claimed is a predictive statistical tree model that overcomes several problems observed in prior statistical models and regression analyses, while ensuring greater accuracy and predictive capabilities. Although the claimed use of the predictive statistical tree model described herein is directed to the prediction of a disease in individuals, the claimed model can be used for a variety of applications including the prediction of disease states, susceptibility of disease states or any other biol. state of interest, as well as other applicable

non-biol. states of interest. This model first **screens** genes to reduce noise, applies kmeans correlation-based clustering targeting a large number of clusters, and then uses singular value decompns. (SVD) to extract the single dominant factor (principal component) from each cluster. This generates a statistically significant number of cluster-derived singular factors, that are referred to as metagenes, that characterize multiple patterns of expression of the genes across samples. The strategy aims to extract multiple such patterns while reducing dimension and smoothing out gene-specific noise through the aggregation within clusters. Formal predictive anal. then uses these metagenes in a Bayesian classification tree anal. This generates multiple recursive partitions of the sample into subgroups (the 'leaves' of the classification tree), and assocs. Bayesian predictive probabilities of outcomes with each subgroup. Overall predictions for an individual sample are then generated by averaging predictions, with appropriate wts., across many such tree models. The model includes the use of iterative out-of-sample, cross-validation predictions leaving each sample out of the data set one at a time, refitting the model from the remaining samples and using it to predict the hold-out case. This rigorously tests the predictive value of a model and mirrors the real-world **prognostic** context where prediction of new cases as they arise is the major goal.

L9 ANSWER 2 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 14 May 2004
ACCESSION NUMBER: 2004:391566 HCAPLUS
DOCUMENT NUMBER: 140:402865
TITLE: Tumor **diagnostic** agent, and its use
INVENTOR(S): Ota, Shigeo; Osawa, Ikuo; Segawa, Tatsuya; Kinoshita, Noriaki
PATENT ASSIGNEE(S): Immuno-Biological Laboratories Co., Ltd., Japan
SOURCE: Jpn. Kokai Tokkyo Koho, 17 pp.
CODEN: JKXXAF
DOCUMENT TYPE: Patent
LANGUAGE: Japanese
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
JP 2004138522	A2	20040513	JP 2002-303893	20021018

PRIORITY APPLN. INFO.: JP 2002-303893 20021018

AB A tumor **diagnostic** agent is provided, with which tumor-related diseases are accurately **diagnosed** with low price in comparison with imaging **diagnosis** or histopathol. test as a conventional **diagnosis** technique for tumor-related diseases. Also provided is a **diagnostic** method for **tumor**-related diseases such as glioma and **bladder tumor** using this **diagnostic** agent. The tumor **diagnostic** agent is characterized in that it contains an antibody capable of recognizing **survivin** .

IT **371761-91-0**, Proteinase inhibitor, **survivin**
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)

(tumor **diagnostic** agent using antibody to **survivin**)

L9 ANSWER 3 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 18 Jan 2004
ACCESSION NUMBER: 2004:41595 HCAPLUS
DOCUMENT NUMBER: 140:109555
TITLE: Genes showing altered expression in cell senescence and their use as markers in **screening** for antitumor drugs
INVENTOR(S): Roninson, Igor B.; Chang, Bey-Dih
PATENT ASSIGNEE(S): The Board of Trustees of the University of Illinois, USA
SOURCE: PCT Int. Appl., 102 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004005462	A2	20040115	WO 2003-US20425	20030627

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2002-394121P P 20020703
AB Genes that are regulated by cell senescence are identified and used as markers in **screening** for agents that induce senescence that may be useful as antitumor agents. The regulatory regions of genes showing senescence-dependent gene expression may be used to drive expression of a reporter gene in a drug **screening assay**. The method can be used in tumor cells or in tumor cell models, specifically in cell lines deficient in p53. These are expected to be capable of killing tumor cells without having the same broad toxicities as current chemotherapeutic agents. Exposure of HCT116 colon carcinoma cells to doxorubicin resulted in the population splitting onto senescent and non-senescent populations. MRNA populations from the two cell types were compared to identify genes showing altered expression in senescence.
IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (expression in senescence of gene for; genes showing altered expression in cell senescence and their use as markers in **screening** for antitumor drugs)

L9 ANSWER 4 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 13 Jan 2004

ACCESSION NUMBER: 2004:24947 HCAPLUS
DOCUMENT NUMBER: 140:251179
TITLE: **Urine Detection** of **Survivin** is a Sensitive Marker for the Noninvasive **Diagnosis** of **Bladder Cancer**
AUTHOR(S): Shariat, Shahrokh F.; Casella, Roberto; Khoddami, Seyed M.; Hernandez, Gina; Sulser, Tullio; Gasser, Thomas C.; Lerner, Seth P.
CORPORATE SOURCE: Scott Department of Urology, Baylor College of Medicine and The Methodist Hospital, Houston, TX, 77030, USA
SOURCE: Journal of Urology (Hagerstown, MD, United States) (2004), 171(2, Pt. 1), 626-630
CODEN: JOURAA; ISSN: 0022-5347
PUBLISHER: Lippincott Williams & Wilkins
DOCUMENT TYPE: Journal
LANGUAGE: English

AB In a preliminary study **urine detection** of **survivin**, an integrator of cell death and mitosis, accurately **detected bladder cancer**. The objectives of this study were to confirm these findings in a large cohort of subjects undergoing cystoscopy, to assess the **diagnostic** performance of **urine survivin** and to test whether evaluation of **urine survivin** adds independent value to **urine** NMP22 (Matritech, Cambridge, Massachusetts) and cytol. for the **detection** of **bladder cancer**. **Urine survivin** was **measured** using a **Bio-Dot** microfiltration **detection** system (Bio-Rad, Hercules, California) in voided **urine** specimens collected before cystoscopy in 117 cases and 92 controls. Bladder washout samples for cytol. were collected in 174 subjects. **Urine** levels of NMP22 were **measured** using a com. available **ELISA**. Higher levels of **urine survivin** were associated with an increased risk of **bladder cancer** ($p < 0.001$) and **tumors** of higher grade ($p = 0.037$), but not with invasive stage, after adjustment for the effects of **urine** cytol., NMP22 and age. The sensitivity, specificity, and pos. and neg. predictive values of **survivin** for the **diagnosis** of **bladder cancer** (64%, 93%, 92% and 67%, resp.), are superior to those of NMP22 and cytol. **Survivin** had the highest specificity and pos. predictive value for the **detection** of **bladder cancer** across each **tumor** stage and grade. **Urine survivin** was a strong, independent predictor of the presence of **bladder cancer** and higher **tumor** grade. **Urine detection** of **survivin** is an accurate **diagnostic** test for **bladder cancer** that retains its efficiency regardless of **cancer** stage and grade.

IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(**survivin** in **urine** as marker for the noninvasive **diagnosis** of **bladder**

cancer)
REFERENCE COUNT: 9 THERE ARE 9 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 5 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 14 Dec 2003
ACCESSION NUMBER: 2003:971787 HCAPLUS
DOCUMENT NUMBER: 140:13770
TITLE: **Diagnosis** and drug **screening** using calibrated gene expression profiles
INVENTOR(S): Bevilacqua, Michael P.; Bankaitis-Davis, Danute M.; Cheronis, John C.; Tryon, Victor
PATENT ASSIGNEE(S): Source Precision Medicine, Inc., USA
SOURCE: U.S. Pat. Appl. Publ., 84 pp., Cont.-in-part of U.S. Ser. No. 605,581, abandoned.
CODEN: USXXCO
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 2
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 2003229455	A1	20031211	US 2001-821850	20010329
US 6692916	B2	20040217		

PRIORITY APPLN. INFO.: US 1999-141542P P 19990628
US 2000-195522P P 20000407
US 2000-605581 B2 20000628

AB A method provides an index that is indicative of the state of a subject, as to a biol. condition, based on a sample from the subject. An embodiment of this method includes: deriving from the sample a profile data set, the profile data set including a plurality of members, each member being a **quant.** **measure** of the amount of a distinct RNA or protein constituent in a panel of constituents selected so that **measurement** of the constituents enables evaluation of the biol. condition; and in deriving the profile data set, achieving such **measure** for each constituent under **measurement** conditions that are substantially repeatable; and applying values from the profile data set to an index function that provides a mapping from an instance of a profile data set into a single-valued **measure** of biol. condition, so as to produce an index pertinent to the biol. condition of the subject. The index was **determined** with resp. to a relevant population which has in common property that is at least one of age group, gender, ethnicity, geog. location, diet,medical disorder, clin. indicator, medication, phys. activity, body mass, and environmental exposure. The biol. conditions include inflammation, diabetes, **prostate** health or disease, manifested skin, liver metabolism and disease, vascular disease, abnormal cell development, **cancer** and infectious disease. The method can be used for evaluating the effect on a biol. condition by drugs.

IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)

(**diagnosis** and drug **screening** using calibrated gene expression profiles)

L9 ANSWER 6 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 04 Dec 2003
ACCESSION NUMBER: 2003:943755 HCAPLUS
DOCUMENT NUMBER: 139:392136
TITLE: Human cancer recurrence **diagnosis** by nucleic acid **hybridization** to **detect** the ratio of pro-apoptosis factor and **survivin** mRNA
INVENTOR(S): Sandler, Anthony D.
PATENT ASSIGNEE(S): University of Iowa Research Foundation, USA
SOURCE: U.S., 16 pp.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
US 6656684	B1	20031202	US 2000-705146	20001102

PRIORITY APPLN. INFO.: US 2000-705146 20001102

AB The present invention provides methods for **diagnosis** of human tumor recurrence by calculating the mRNA ratio of **Survivin** and pro-apoptosis factor (PAF). The PAF may be Fas, BID, p53, DR4, DR5, or Tumor necrosis factor receptor. **Survivin** and pro-apoptosis factor specific oligonucleotides were **labeled** to **determine** the amount of **survivin** and PAF mRNA by nucleic acid **hybridization**. **Survivin**:PAF ratio of more than 1.5 is predictive that the tumor may recur.

IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(gene for; human cancer recurrence **diagnosis** by nucleic acid **hybridization** to **detect** the ratio of pro-apoptosis factor and **survivin** mRNA)

REFERENCE COUNT: 25 THERE ARE 25 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 7 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 13 Nov 2003
ACCESSION NUMBER: 2003:887375 HCAPLUS
DOCUMENT NUMBER: 140:143566
TITLE: Recursive Partitioning as an Approach to Selection of Immune Markers for Tumor **Diagnosis**
AUTHOR(S): Koziol, James A.; Zhang, Jian-Ying; Casiano, Carlos A.; Peng, Xuan-Xian; Shi, Fu-Dong; Feng, Anne C.; Chan, Edward K. L.; Tan, Eng M.
CORPORATE SOURCE: Division of Biomathematics, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Clinical Cancer Research (2003), 9(14), 5120-5126
CODEN: CCREF4; ISSN: 1078-0432

PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Cancer **sera** contain antibodies which react with a unique group of autologous cellular antigens called tumor-associated antigens (TAAs), but the low frequency of pos. reactions against any individual antigen has precluded use of autoantibodies as useful **diagnostic** markers. With **enzyme immunoassay**, the authors examined antibody frequencies to a panel of 7 TAAs, c-myc, cyclin B1, IMP1, Koc, p53, p62, and **survivin**, in 527 **cancer** patients (64 **breast cancer** patients, 45 **colorectal cancers**, 91 gastric **cancers**, 65 hepatocellular **carcinomas**, 56 **lung cancers**, and 206 **prostate cancers**), and 346 normals. The authors used recursive partitioning to assess whether they could accurately classify individuals as either cancer patients or normals on the basis of the profile of antibody reactivity to the 7 TAAs for each individual. Recursive partitioning resulted in the selection of subsets of the 7-panel TAA, which differentiated between tumors and controls, and these subsets were unique to each cancer cohort. The classification trees had sensitivities ranging from 0.77 to 0.92 and specificities ranging from 0.85 to 0.91 in the cancer cohorts when normal means +2 SDs were used as standard cutoffs for **immunoassay** positivity. Antibody to cyclin B1 was the initial discriminating node for gastric and **lung cancers**, and for hepatocellular **carcinoma**, and was a subsequent discriminating node in all of the other **cancer** cohorts. C-myc was the initial discriminating node in **breast cancer**, p62 in **prostate cancer**, and IMP1 in colon **cancer**. Recursive partitioning demonstrated that no more than 3 of the 7 TAAs were needed for any cancer cohort to arrive at these levels of sensitivity and specificity. This initial study shows that multiple antigen miniarrays can provide accurate and valuable tools for cancer **detection** and **diagnosis**. Performance of the miniarrays might be enhanced by other combinations of TAAs appropriately selected for different cancer cohorts.
IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(recursive partitioning as approach to selection of markers for tumor **diagnosis**)
REFERENCE COUNT: 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 8 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 29 Jun 2003
ACCESSION NUMBER: 2003:492205 HCAPLUS
DOCUMENT NUMBER: 139:64332
TITLE: Methods for production of biochips and their use in cancer **diagnosis** and treatment
INVENTOR(S): Bignon, Yves Jean; Vidal, Veronique
PATENT ASSIGNEE(S): Centre Medico Chirurgical De Tronquieres, Fr.
SOURCE: Fr. Demande, 79 pp.

CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2833969	A1	20030627	FR 2001-16963	20011220

PRIORITY APPLN. INFO.: FR 2001-16963 20011220

AB The present invention aims at manufacturing biochips of very high quality and their use in gene expression profiling for cancer **diagnosis** and therapy in mammals.

IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(methods for production of biochips and their use in cancer **diagnosis** and treatment)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 9 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 29 Jun 2003
ACCESSION NUMBER: 2003:492204 HCAPLUS
DOCUMENT NUMBER: 139:64331
TITLE: Modular biochip arrays and their **diagnostic** or analytical uses and their preparation and uses
INVENTOR(S): Bignon, Yves Jean; Vidal, Veronique; D'Incan, Chantal; Laplace, Chambaud Valerie; Sylvain, Vidal Valerie
PATENT ASSIGNEE(S): Centre Medico Chirurgical De Tronquieres, Fr.
SOURCE: Fr. Demande, 124 pp.
CODEN: FRXXBL
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
FR 2833968	A1	20030627	FR 2001-16962	20011220

PRIORITY APPLN. INFO.: FR 2001-16962 20011220

AB A method of constructing microarrays for specific **diagnostic** or research purposes is described. The microarrays are made up of modular sections with each module containing probes for a defined set of genes that can be assembled to give an array suitable for a specific purposes. The individual modules may be on sep. supports.

IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(as indicator in **breast cancer diagnosis**; modular biochip arrays and their **diagnostic** or anal. uses and their preparation and uses)

REFERENCE COUNT: 13 THERE ARE 13 CITED REFERENCES AVAILABLE

FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 10 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 16 May 2003
ACCESSION NUMBER: 2003:377082 HCAPLUS
DOCUMENT NUMBER: 138:380512
TITLE: Systems and methods for characterizing a biological condition or agent using calibrated gene expression profiles
INVENTOR(S): Bevilacqua, Michael; Cheronis, John C.; Tryon, Victor
PATENT ASSIGNEE(S): Source Precision Medicine, Inc., USA
SOURCE: PCT Int. Appl., 156 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003040404	A1	20030515	WO 2002-US36084	20021108
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2003219771	A1	20031127	US 2002-291856	20021108

PRIORITY APPLN. INFO.:
US 2001-348213P P 20011109
US 2001-340881P P 20011207
US 2002-369633P P 20020403
US 2002-376997P P 20020430

AB A method provides an index that is indicative of the state of a subject, as to a biol. condition, based on a sample from the subject. An embodiment of this method includes: deriving from the sample a profile data set, the profile data set including a plurality of members, each member being a **quant.** **measure** of the amount of a distinct RNA or protein constituent in a panel of constituents selected so that **measurement** of the constituents enables evaluation of the biol. condition; and in deriving the profile data set, achieving such **measure** for each constituent under **measurement** conditions that are substantially repeatable; and applying values from the profile data set to an index function that provides a mapping from an instance of a profile data set into a single-valued **measure** of biol. condition, so as to produce an index pertinent to the biol. condition of the subject. The index was **determined** with resp. to a relevant population which has in common property that is at least one of age group, gender, ethnicity, geog. location,

diet,medical disorder, clin. indicator, medication, phys. activity, body mass, and environmental exposure. The biol. conditions include inflammation, diabetes, **prostate** health or disease, manifested skin, liver metabolism and disease, vascular disease, abnormal cell development, **cancer** and infectious disease. The method can be used for evaluating the effect on a biol. condition by drugs.

IT **371761-91-0, Survivin**
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(systems and methods for characterizing a biol. condition or agent using calibrated gene expression profiles)

REFERENCE COUNT: 8 THERE ARE 8 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 11 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 12 Feb 2003
ACCESSION NUMBER: 2003:107699 HCAPLUS
DOCUMENT NUMBER: 138:270003
TITLE: Enhancement of Antibody **Detection** in Cancer Using Panel of Recombinant Tumor-associated Antigens
AUTHOR(S): Zhang, Jian-Ying; Casiano, Carlos A.; Peng, Xuan-Xian; Koziol, James A.; Chan, Edward K. L.; Tan, Eng M.
CORPORATE SOURCE: W.M. Keck Autoimmune Disease Center, The Scripps Research Institute, La Jolla, CA, 92037, USA
SOURCE: Cancer Epidemiology, Biomarkers & Prevention (2003), 12(2), 136-143
CODEN: CEBPE4; ISSN: 1055-9965
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Cancer **sera** contain antibodies which react with a unique group of autologous cellular antigens called tumor-associated antigens (TAAs). This study **dets.** whether a mini-array of multiple TAAs would enhance antibody **detection** and be a useful approach to cancer **detection** and **diagnosis.** The mini-array of TAAs comprised full-length recombinant proteins expressed from cDNAs encoding c-myc, p53, cyclin B1, p62, Koc, IMP1, and **survivin.** **Enzyme immunoassay** was used to **detect** antibodies in 527 **sera** from six different types of cancer. Antibody frequency to any individual TAA was variable but rarely exceeded 15-20%. With the successive addition of TAAs to a final total of seven antigens, there was a stepwise increase of pos. antibody reactions up to a range of 44-68%. **Breast, lung,** and **prostate** **cancer** patients showed sep. and distinct profiles of reactivity, suggesting that uniquely constituted antigen mini-arrays might be developed to distinguish between some types of **cancer.** Distinct antibody profiles were not observed in gastric, **colorectal,** and hepatocellular **carcinomas** with this set of seven TAAs. **Detection** of autoantibodies in cancer can be enhanced by using a mini-array of several TAAs as target antigens. Addnl. studies in early cancer patients and

high-risk individuals and the design of unique antigen panels for different cancers would help to **determine** whether multiple antigen mini-arrays for the **detection** of autoantibodies might contribute a clin. useful noninvasive approach to cancer **detection** and **diagnosis**.

IT **371761-91-0, Survivin.**
RL: ARU (Analytical role, unclassified); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(enhancement of antibody **detection** in cancer **diagnosis** using panel of recombinant tumor-associated antigens)

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 12 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 27 Jan 2003
ACCESSION NUMBER: 2003:61264 HCAPLUS
DOCUMENT NUMBER: 139:143215
TITLE: Multiplex gene expression analysis for high-throughput drug discovery: **screening** and analysis of compounds affecting genes over-expressed in cancer cells
AUTHOR(S): Johnson, Paul H.; Walker, Roger P.; Jones, Steven W.; Stephens, Kathy; Meurer, Janet; Zajchowski, Deborah A.; Luke, May M.; Eeckman, Frank; Tan, Yuping; Wong, Linda; Parry, Gordon; Morgan, Thomas K., Jr.; McCarrick, Meg A.; Monforte, Joseph
CORPORATE SOURCE: Department of Cancer Research, Berlex Biosciences, Richmond, CA, 94804-0099, USA
SOURCE: Molecular Cancer Therapeutics (2002), 1(14), 1293-1304
CODEN: MCTOCF; ISSN: 1535-7163
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Drug discovery strategies are needed that can rapidly exploit multiple therapeutic targets associated with the complex gene expression changes that characterize a polygenic disease such as cancer. We report a new cell-based high-throughput technol. for **screening** chemical libraries against several potential cancer target genes in parallel. Multiplex gene expression (MGE) anal. provides direct and **quant. measurement** of multiple endogenous mRNAs using a multiplexed **detection** system coupled to **reverse transcription-PCR**. A multiplex **assay** for six genes over-expressed in **cancer** cells was used to **screen** 9000 chems. and known drugs in the human **prostate cancer** cell line PC-3. Active compds. that modulated gene expression levels were identified, and IC50 values were **detd**. for compds. that bind DNA, cell surface receptors, and components of intracellular signaling pathways. A class of steroids related to the cardiac glycosides was identified that potently inhibited the **plasma** membrane Na+K+-ATPase resulting in the inhibition of four of the prostate target genes including transcription factors

Hoxb-13, hPSE/PDEF, hepatocyte nuclear factor-3α, and the inhibitor of apoptosis, **survivin**. Representative compds. selectively induced apoptosis in PC-3 cells compared with the non-metastatic cell line BPH-1. The multiplex **assay** distinguished potencies among structural variants, enabling structure-activity anal. suitable for chemical optimization studies. A second multiplex **assay** for five toxicol. markers, Hsp70, Gadd153, Gadd45, O6-methylguanine-DNA methyltransferase, and cyclophilin, **detected** compds. that caused DNA damage and cellular stress and was a more sensitive and specific indicator of potential toxicity than **measurement** of cell viability. MGE anal. facilitates rapid drug **screening** and compound optimization, the simultaneous **measurement** of toxicol. end points, and gene function anal.

IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); BIOL (Biological study) (multiplex gene expression anal. for high-throughput drug discovery)

REFERENCE COUNT: 46 THERE ARE 46 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 13 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 26 Jul 2002
ACCESSION NUMBER: 2002:555762 HCAPLUS
DOCUMENT NUMBER: 137:121595
TITLE: **Detection** of **survivin** in the biological fluids of cancer patients
INVENTOR(S): Altieri, Dario C.; Weiss, Robert M.; Smith, Shannon D.; Wheeler, Marcia A.; Plescia, Janet
PATENT ASSIGNEE(S): Yale University, USA
SOURCE: PCT Int. Appl., 41 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2002057787	A2	20020725	WO 2002-US574	20020111
WO 2002057787	A3	20021219		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG				
US 2002160395	A1	20021031	US 2002-42302	20020111
EP 1350114	A2	20031008	EP 2002-714720	20020111
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC,				

PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR
PRIORITY APPLN. INFO.: US 2001-260898P P 20010112
WO 2002-US574 W 20020111

AB The present invention includes a method for **diagnosing** cancer comprising **detecting** the presence of **survivin** in the biol. fluid of a patient. The present invention also provides kits comprising one or more agents that **detect survivin** polypeptide or **survivin** nucleic acid and a container for collecting biol. fluid for testing.

IT **371761-91-0, Survivin**
RL: ANT (Analyte); DGN (Diagnostic use); ANST (Analytical study); BIOL (Biological study); USES (Uses)
(**detection** of **survivin** in biol. fluids of cancer patients)

L9 ANSWER 14 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 27 Mar 2002
ACCESSION NUMBER: 2002:229863 HCAPLUS
DOCUMENT NUMBER: 137:138159
TITLE: **Bladder cancer** **detection** with urinary **survivin**, an inhibitor of apoptosis
AUTHOR(S): Sharp, Jennifer D.; Hausladen, Derek A.; Maher, M. Grey; Wheeler, Marcia A.; Altieri, C.; Weiss, Robert M.
CORPORATE SOURCE: Department of Surgery (Section of Urology) and Pathology (Boyer Center for Molecular Medicine), Yale University School of Medicine, New Haven, CT, USA
SOURCE: Frontiers in Bioscience [online computer file] (2002), 7, E36-E41
CODEN: FRBIF6; ISSN: 1093-4715
URL: http://www.bioscience.org/2002/v7/e/sharp/pdf.pdf
PUBLISHER: Frontiers in Bioscience
DOCUMENT TYPE: Journal; General Review; (online computer file)
LANGUAGE: English

AB A review. The current "gold standard" for the **diagnosis** of **bladder cancer** is cystoscopy and **urine** cytol. Cystoscopy, a naked eye assessment of the bladder, is invasive, uncomfortable and costly while cytol. has high specificity but low sensitivity (40-60%) particularly for low-grade lesions. Therefore, there is a need for a mol. tumor marker **assay** that is simple to perform and sensitive, particularly for low-grade lesions. By looking to the pathophysiol. of **bladder cancer**, we identified **survivin**, an inhibitor of apoptosis that is not generally expressed in fully differential adult tissue and is highly expressed in **bladder cancer**. **Survivin** is **detected** in whole **urine** of patients with TCC using a simple antibody based test. The sensitivity of **survivin** testing for new or recurrent **bladder cancer** is 100% while the specificity for other **neoplastic** and non-**neoplastic genitourinary** disease is 95%. The high sensitivity of this simple, noninvasive test is well suited to **bladder cancer**, a disease with high rates of

recurrence.

IT **371761-91-0, Survivin**
RL: BSU (Biological study, unclassified); DGN (Diagnostic use); BIOL (Biological study); USES (Uses)
(**bladder cancer detection** with urinary **survivin**, an inhibitor of apoptosis)

REFERENCE COUNT: 23 THERE ARE 23 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 15 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 30 Oct 2001
ACCESSION NUMBER: 2001:785622 HCAPLUS
DOCUMENT NUMBER: 135:314495
TITLE: Differentially expressed nucleic acids encoding tumor-associated proteins, kits, and methods for identification, assessment, prevention, and therapy of human prostate cancer
INVENTOR(S): Schlegel, Robert; Endege, Wilson; Monahan, John E.
PATENT ASSIGNEE(S): Millennium Predictive Medicine, Inc., USA
SOURCE: PCT Int. Appl., 975 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 4
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001053836	A2	20010726	WO 2001-XC2318	20010124
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
WO 2001053836	A2	20010726	WO 2001-US2318	20010124
WO 2001053836	A3	20020606		
WO 2001053836	C2	20021107		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				

PRIORITY APPLN. INFO.:

US 2000-178525P	P	20000124
US 2000-183245P	P	20000217
US 2000-190139P	P	20000316
US 2000-208126P	P	20000531
US 2000-219705P	P	20000718
US 2000-255160P	P	20001213
WO 2001-US2318	A	20010124

AB This invention relates to newly discovered correlations between expression of certain nucleic acid markers and the cancerous state of human prostate cells. The levels of expression of individual markers and combinations of markers described herein correlates with the presence of prostate cancer or a pre-malignant condition in a patient. Methods are provided for detecting the presence of prostate cancer in a sample, the absence of prostate cancer in a sample, the stage of a prostate cancer, the metastatic potential of a prostate cancer, the indolence or aggressiveness of the cancer, and other characteristics of prostate cancer that are relevant to prevention, diagnosis, characterization and therapy of prostate cancer in a patient. Thousands of differentially-expressed cDNA markers are identified in subtracted cDNA libraries and by transcript profiling. [This abstract record is the fourth of four records for this document necessitated by the large number of index entries required to fully index the document and publication system constraints.].

L9 ANSWER 16 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 30 Aug 2001
ACCESSION NUMBER: 2001:630235 HCAPLUS
DOCUMENT NUMBER: 135:342957
TITLE: **Detection** of anti-**survivin** antibody in gastrointestinal cancer patients
AUTHOR(S): Yagihashi, Atsuhito; Asanuma, Koichi; Nakamura, Masashi; Araya, Jan; Mano, Yoshinori; Torigoe, Torigoe; Kobayashi, Daisuke; Watanabe, Naoki
CORPORATE SOURCE: Department of Clinical Laboratory Medicine, Sapporo Medical University School of Medicine, Sapporo, 060-8543, Japan
SOURCE: Clinical Chemistry (Washington, DC, United States) (2001), 47(9), 1729-1731
CODEN: CLCHAU; ISSN: 0009-9147
PUBLISHER: American Association for Clinical Chemistry
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The occurrence of antibody response against **survivin** in various gastrointestinal cancer patients was examined **Blood** samples from 33 healthy **blood** donors and 63 gastrointestinal cancer patients after histol. **diagnosis** were studied. No increase in the overall prevalence of antibody reactivity was observed in the addition of anti-p53 antibodies. **Survivin** expression was **detected** in **colorectal cancers**, and mRNA transcripts encoding **survivin** were **detected** in recurrent **colorectal cancers** by a **reverse transcriptase-polymerase chain** reaction. Antibody responses against **survivin** were not always apparent in all patients whose cancers expressed **survivin**.

Anti-**survivin** reactivity was influenced by the site of tumor origin.

IT **371761-91-0, Survivin**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(anti-**survivin** antibodies in human gastrointestinal cancer)

REFERENCE COUNT: 12 THERE ARE 12 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 17 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 27 Jul 2001
ACCESSION NUMBER: 2001:545905 HCAPLUS
DOCUMENT NUMBER: 135:133094
TITLE: Real-time **RT-PCR** for **detecting survivin** oncogene mRNA in human samples, and its use in **diagnosis** of neoplastic, hyperplastic, cytologically dysplastic and/or premalignant cellular growth
INVENTOR(S): Nichols, W. Stephen; Chan, Raymond C. K.; Jouben-Steele, Lisa
PATENT ASSIGNEE(S): Cedars-Sinai Medical Center, USA
SOURCE: PCT Int. Appl., 29 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001053535	A2	20010726	WO 2001-US1956	20010119
WO 2001053535	A3	20020808		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 2000-488191 A 20000120

AB The invention provides the use of real-time **reverse transcription-polymerase chain** reaction (**RT-PCR**), using **survivin** oncogene-specific primers and probes, for **detecting** neoplastic, hyperplastic, cytol. dysplastic and/or premalignant cellular growth or proliferation in a human subject. The invention relates that the **RT-PCR** can be done on a human bodily substance, such as **urine, blood**, semen, saliva, mucus, feces, or cellular material. The invention also

relates that overexpression of nucleic acids (mRNA) or protein products of the **survivin** oncogene is **diagnostic** for neoplastic, hyperplastic, cytol. dysplastic and/or premalignant cellular growth or proliferation. The invention also provides provides the sequences of said **survivin** oncogene-specific primers and probes, and **diagnostic** kits containing them. Further, the invention specifically presents the use of real-time **RT-PCR** in **detecting survivin** oncogene in the urinary tract of individuals, and in **detection** of urinary tract neoplasms. In the example section, the invention discussed that products of **RT-PCR** can be **detected** using **hybridization dot blot** or nested-PCR.

L9 ANSWER 18 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 11 May 2001
ACCESSION NUMBER: 2001:338762 HCAPLUS
DOCUMENT NUMBER: 134:362292
TITLE: Methods of **determining** individual hypersensitivity to a pharmaceutical agent from gene expression profile
INVENTOR(S): Farr, Spencer
PATENT ASSIGNEE(S): Phase-1 Molecular Toxicology, USA
SOURCE: PCT Int. Appl., 222 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2001032928	A2	20010510	WO 2000-US30474	20001103
WO 2001032928	A3	20020725		

W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM
RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG

PRIORITY APPLN. INFO.: US 1999-165398P P 19991105
US 2000-196571P P 20000411

AB The invention discloses methods, gene databases, gene arrays, protein arrays, and devices that may be used to **determine** the hypersensitivity of individuals to a given agent, such as drug or other chemical, in order to prevent toxic side effects. In one embodiment, methods of identifying hypersensitivity in a subject by obtaining a gene expression profile of multiple genes associated with hypersensitivity of the subject suspected to be hypersensitive, and identifying in the gene expression profile of the subject a pattern of gene expression of the genes associated with hypersensitivity are

disclosed. The gene expression profile of the subject may be compared with the gene expression profile of a normal individual and a hypersensitive individual. The gene expression profile of the subject that is obtained may comprise a profile of levels of mRNA or cDNA. The gene expression profile may be obtained by using an array of nucleic acid probes for the plurality of genes associated with hypersensitivity. The expression of the genes predetd. to be associated with hypersensitivity is directly related to prevention or repair of toxic damage at the tissue, organ or system level. Gene databases arrays and apparatus useful for identifying hypersensitivity in a subject are also disclosed.

L9 ANSWER 19 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 29 Jan 2001
ACCESSION NUMBER: 2001:65575 HCAPLUS
DOCUMENT NUMBER: 135:31997
TITLE: **Urine detection** of **survivin** and **diagnosis** of **bladder cancer**
AUTHOR(S): Smith, Shannon D.; Wheeler, Marcia A.; Plescia, Janet; Colberg, John W.; Weiss, Robert M.; Altieri, Dario C.
CORPORATE SOURCE: Boyer Center for Molecular Medicine, Yale University School of Medicine, New Haven, CT, 06536, USA
SOURCE: JAMA, the Journal of the American Medical Association (2001), 285(3), 324-328
CODEN: JAMAAP; ISSN: 0098-7484
PUBLISHER: American Medical Association
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Context Dysregulation of apoptosis may favor onset and progression of cancer and influence response to therapy. **Survivin** is an inhibitor of apoptosis that is selectively overexpressed in common human cancers, but not in normal tissues, and that correlates with aggressive disease and unfavorable outcomes. Objective To investigate the potential suitability of **survivin** **detection** in **urine** as a novel predictive/ **prognostic** mol. marker of **bladder cancer** . Design, Setting, and Patients Survey of **urine** specimens from 5 groups: healthy volunteers (n=17) and patients with nonneoplastic urinary tract disease (n=30), **genitourinary** **cancer** (n=30), new-onset or recurrent **bladder** **cancer** (n=46), or treated **bladder cancer** (n=35), recruited from 2 New England urol. clinics. Main Outcome **Measures Detectable survivin** levels, analyzed by a novel **detection** system and confirmed by Western blot and **reverse transcriptase** **polymerase chain** reaction (**RT-** **PCR**), in **urine** samples of the 5 participant groups. Results **Survivin** was **detected** in the **urine** samples of all 46 patients with new or recurrent **bladder cancer** using a novel **detection** system (31 of 31) and **RT-PCR** (15 of 15) methods. **Survivin** was not **detected** in the **urine** samples of 32 of 35 patients treated for **bladder**

cancer and having neg. cystoscopy results. None of the healthy volunteers or patients with **prostate, kidney,** vaginal, or cervical **cancer** had **detectable survivin** in **urine** samples. Of the 30 patients with nonneoplastic urinary tract disease, **survivin** was **detected** in 3 patients who had bladder abnormalities noted using cystoscopy and in 1 patient with an increased prostate-specific antigen level. Patients with low-grade **bladder cancer** had significantly lower **urine survivin** levels than patients with **carcinoma** in situ (P=.002). Conclusions Highly sensitive and specific **determination** of **urine survivin** appears to provide a simple, noninvasive **diagnostic** test to identify patients with new or recurrent **bladder cancer.**

REFERENCE COUNT: 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L9 ANSWER 20 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 05 May 2000
ACCESSION NUMBER: 2000:289792 HCAPLUS
DOCUMENT NUMBER: 133:246912
TITLE: Molecular biology of multidrug resistance (MDR) in ovarian cancers and novel method of **detecting** developing MDR in vitro
AUTHOR(S): Sakamoto, Hideki
CORPORATE SOURCE: Dep. Obstetrics Gynecology, Nihon Univ. Sch. Med., Tokyo, Japan
SOURCE: Nippon Sanka Fujinka Gakkai Zasshi (1999), 51(8), 549-561
CODEN: NISFAY; ISSN: 0300-9165
PUBLISHER: Nippon Sanka Fujinka Gakkai
DOCUMENT TYPE: Journal
LANGUAGE: Japanese

AB Acquisition of multidrug resistance (MDR) phenotype in ovarian cancers is the main obstacle in successful improvement of the treatment strategies. Currently, putative two MDR pathways have been proposed. First is membrane associated drug efflux pump such as MDR-1 and MRP or LRP (Type 1 MDR factor). Second is anti-apoptosis proteins such as p53, Bcl-2 and **survivin** (Type 2 MDR factor). In addition to these factors, we have studied DNA repair **enzyme** ERCC-1, microsatellite instability (MI) and c-erbB-2 amplification (Type 3 MDR factors) in 62 (stage I, II, Ill, IV = 18, 9, 20, 15) ovarian cancer cases. Also **plasma** free telomere fragments are **monitored** before and after chemotherapy to test its **diagnostic** potential for early **detection** of MDR phenotype. The expression of type 1, 2, 3 MDR factors are equally seen in serous, mucinous, endometrioid and clear cell cancers. The MDR-1 and LRP were more frequently seen in advanced stages (III + IV) than early stages (I + II) .Survival anal. by the Cox proportional hazard model showed over expression of mutant p53 (RR = 3.3, p<0.006), **survivin** (RR = 6.2, p<0.008) and amplification of c-erbB-2 (RR = 2.0, p<0.01) were stage-independent risk factors. On the other hand, the progression free intervals (PFI) were affected by MDR-1 (RR = 5.6, p<0.02) and

LRP (RR = 16.8, p<0.004).Expression of MDR-1 and LRP pos. correlated with later development of MDR phenotype whereas type 2 has no impact on the MDR. Type 3 factors all pos. correlated with the MDR phenotype after recurrence (ERCC-1: RR = 2, p<0.001, MI: RR = 1.5, p<0.05, c-erbB-2: RR = 2.0, p<0.002). Chronol. of MDR related factor expression was tested longitudinally in primary, early metastatic and late recurrent lesions of the same patients (n = 19). The anal. showed frequency of MDR-1 expression, MI and c-erbB-2 amplification have been increased in late recurrent lesions whereas LRP and **survivin** have already been expressed in the primary lesions. These observation indicate that drug efflux pumps are related with recurrence and resistance but MDR-1 and MRP are associated with acquired resistance but LRP with primary resistance. The p53 and **survivin** are strong neg. indicator for survival but have little impact on recurrence. ERCC-1, MI and c-erbB-2 do have relationship with recurrence and resistance. Lastly free telomere fragments are successfully **detected** in the peripheral **blood** and the pos. predictive value for discriminating chemotherapy responders from non-responders was 0.83 whereas **serum** tumor markers had that of 0.52. This is the first report of chronol. in MDR and MDR-related genes expressions in ovarian cancer. The distinct association of each MDR-related factors with clin. parameters indicates independent roles of these factors and thus potential use of the factors as target for mol. treatments of ovarian cancer.

L9 ANSWER 21 OF 21 HCAPLUS COPYRIGHT 2004 ACS on STN
ED Entered STN: 19 Apr 2000
ACCESSION NUMBER: 2000:248476 HCAPLUS
DOCUMENT NUMBER: 132:249763
TITLE: Antibody response to the tumor-associated inhibitor of apoptosis protein **survivin** in cancer patients
AUTHOR(S): Rohayem, Jacques; Diestelkoetter, Petra; Weigle, Bernd; Oehmichen, Antje; Schmitz, Marc; Mehlhorn, Juergen; Conrad, Karsten; Rieber, Ernst Peter
CORPORATE SOURCE: Institute for Immunology, Medical Faculty, Technical University of Dresden, Dresden, 01101, Germany
SOURCE: Cancer Research (2000), 60(7), 1815-1817
CODEN: CNREA8; ISSN: 0008-5472
PUBLISHER: American Association for Cancer Research
DOCUMENT TYPE: Journal
LANGUAGE: English
AB Antibody reactivity against **survivin**, a recently identified **tumor**-associated protein, was **determined** in **sera** from patients with **lung** (n = 51) or **colorectal cancer** (n = 49). The same collection of **sera** was tested for the presence of antibodies against p53. Eleven **sera** from **lung cancer** patients and four **sera** from **colorectal cancer** patients reacted with purified recombinant **survivin** in an **ELISA** (21.6% and 8.2%, resp.), whereas four **sera** from **lung cancer** patients and nine **sera** from **colorectal**

cancer patients contained anti-p53 antibodies (7.8% and 18.4%, resp.). The increase in prevalence when anti-**survivin** and anti-p53 antibodies were **determined** in parallel was statistically significant (29.4% vs. 7.8%, P = 0.005 in **lung cancer** population; 26.6% vs. 8.2%, P = 0.015 in **colorectal cancer** population). The high prevalence of anti-**survivin** antibodies makes these antibodies an attractive novel marker for the **diagnosis** of **lung** and **colorectal cancer**, particularly in patients lacking anti-p53 antibodies.

REFERENCE COUNT: 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

(FILE 'MEDLINE, BIOSIS, EMBASE, WPIDS, CONFSCI, SCISEARCH, JICST-EPLUS, JAPIO, CANCERLIT' ENTERED AT 12:27:35 ON 22 JUN 2004)

L10 64 S L9

L11 38 DUP REM L10 (26 DUPLICATES REMOVED)

L11 ANSWER 1 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2004-404897 [38] WPIDS

DOC. NO. NON-CPI: N2004-322541

DOC. NO. CPI: C2004-152167

TITLE: **Tumor diagnostic** agents useful for immune-tissue staining of **tumor** cells and for **diagnosing** glioma and **bladder cancer**, containing **survivin** specific antibodies.

DERWENT CLASS: B04 D16 S03

PATENT ASSIGNEE(S): (MENE-N) MENEKI SEIBUTSU KENKYUSHO KK

COUNTRY COUNT: 1

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
JP 2004138522	A	20040513	(200438)*		17

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
JP 2004138522	A	JP 2002-303893	20021018

PRIORITY APPLN. INFO: JP 2002-303893 20021018

AN 2004-404897 [38] WPIDS

AB JP2004138522 A UPAB: 20040616

NOVELTY - A tumor-**diagnostic** agent (I) containing an antibody which recognizes **survivin**, is new

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are included for: (1) tumor **diagnostic** kit (II) comprising a first reagent containing antibody capable of recognizing **survivin** and a second reagent containing an antibody specific to the antibody which recognizes **survivin** or comprising a first reagent containing antibody recognizing **survivin** and second **labeled** antibody and third antibody capable of recognizing

epitope of first reagent, where one of the antibody of the reagent is immobilized;

(2) **determining** malignancy of glioma, involves carrying out immune-tissue staining of the **survivin** in the brain tissue, **measuring** subsequently the ratio of **survivin** positive cell number with respect to all observation cells and **determining** the malignancy of glioma from the value; and

(3) **diagnosing bladder cancer,** involves **detecting survivin** in a **urine** sample.

USE - (I) is useful for immune-tissue staining of **tumor** cells. (I) and (II) are useful for **diagnosing** glioma or **bladder cancer** (claimed).

ADVANTAGE - (I) and (II) enables convenient and efficient **diagnosis** of **tumor** associated diseases such as glioma and **bladder cancer**. The malignancy of glioma can be **determined** efficiently.

DESCRIPTION OF DRAWING(S) - The figure shows graph representing the relationship between the produced **survivin** index and the malignancy of glioma.

Dwg.3/4

L11 ANSWER 2 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2004:114394 BIOSIS
DOCUMENT NUMBER: PREV200400115653
TITLE: Guanine nucleotide depletion triggers cell cycle arrest and apoptosis in human **neuroblastoma** cell lines.
AUTHOR(S): Messina, Elisa; Gazzaniga, Paola; Micheli, Vanna; Guaglianone, Maria Rosaria; Barbato, Silvia; Morrone, Stefania; Frati, Luigi; Agliano, Anna Maria; Giacomello, Alessandro [Reprint Author]
CORPORATE SOURCE: Department of Experimental Medicine and Pathology, University of Rome, "La Sapienza,", Via Regina Elena 324, 00161, Rome, Italy
Alessandro.Giacomello@uniroma1.it
SOURCE: International Journal of Cancer, (1 March 2004) Vol. 108, No. 6, pp. 812-817. print.
CODEN: IJCNAW. ISSN: 0020-7136.
DOCUMENT TYPE: Article
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Feb 2004
Last Updated on STN: 25 Feb 2004

AB Mycophenolic acid (MPA) specifically inhibits inosine-5'-monophosphate dehydrogenase, the first committed step toward GMP biosynthesis. In its morpholinoethyl ester pro-drug form it is one of the most promising immunosuppressive drugs recently developed. The aim of the present study was to investigate the in vitro effects of MPA, at concentrations readily attainable during immunosuppressive therapy, on 3 human **neuroblastoma** cell lines (LAN5, SHEP and IMR32). Mycophenolic acid (0.1-10 muM) caused a decrease of intracellular levels of guanine nucleotides, a G1 arrest and a time- and dose-dependent death by apoptosis. These effects, associated with an up-regulation of p53, p21 and bax, a

shuttling of p53 protein into the nucleus and a down-regulation of bcl-2, **survivin** and p27 protein, were reversed by the simultaneous addition of guanine or guanosine and were more evident using nondialysed **serum** containing hypoxanthine. These results suggest that in **neuroblastoma** cell lines clinically attainable concentrations of mycophenolic acid deplete guanine nucleotide pools triggering G1 arrest and apoptosis through p53-mediated pathways, indicating a potential role of its morpholinoethyl ester pro-drug in the management of patients with neuroectodermal tumors.

L11 ANSWER 3 OF 38 MEDLINE on STN DUPLICATE 1
ACCESSION NUMBER: 2004033041 MEDLINE
DOCUMENT NUMBER: PubMed ID: 14713774
TITLE: **Urine detection** of **survivin** is a sensitive marker for the noninvasive **diagnosis** of **bladder cancer.**
AUTHOR: Shariat Shahrokh F; Casella Roberto; Khoddami Seyed M; Hernandez Gina; Sulser Tullio; Gasser Thomas C; Lerner Seth P
CORPORATE SOURCE: Scott Department of Urology, Baylor College of Medicine and The Methodist Hospital, Houston, Texas 77030, USA.
SOURCE: Journal of urology, (2004 Feb) 171 (2 Pt 1) 626-30. Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200402
ENTRY DATE: Entered STN: 20040122
Last Updated on STN: 20040302
Entered Medline: 20040226

AB PURPOSE: In a preliminary study **urine detection** of **survivin**, an integrator of cell death and mitosis, accurately **detected bladder cancer.** The objectives of this study were to confirm these findings in a large cohort of subjects undergoing cystoscopy, to assess the **diagnostic** performance of **urine survivin** and to test whether evaluation of **urine survivin** adds independent value to **urine** NMP22 (Matritech, Cambridge, Massachusetts) and cytology for the **detection** of **bladder cancer.** MATERIALS AND METHODS: **Urine survivin** was **measured** using a **Bio-Dot** microfiltration **detection** system (Bio-Rad, Hercules, California) in voided **urine** specimens collected before cystoscopy in 117 cases and 92 controls. Bladder washout samples for cytology were collected in 174 subjects. **Urine** levels of NMP22 were **measured** using a commercially available **enzyme**-linked immunosorbent **assay.** RESULTS: Higher levels of **urine survivin** were associated with an increased risk of **bladder cancer** ($p < 0.001$) and **tumors** of higher grade ($p = 0.037$), but not with invasive stage, after adjustment for the effects of **urine** cytology, NMP22 and

age. The sensitivity, specificity, and positive and negative predictive values of **survivin** for the **diagnosis** of **bladder cancer** (64%, 93%, 92% and 67%, respectively), are superior to those of NMP22 and cytology. **Survivin** had the highest specificity and positive predictive value for the **detection** of **bladder cancer** across each **tumor** stage and grade. CONCLUSIONS: **Urine survivin** was a strong, independent predictor of the presence of **bladder cancer** and higher **tumor** grade. **Urine detection** of **survivin** is an accurate **diagnostic** test for **bladder cancer** that retains its efficiency regardless of **cancer** stage and grade.

L11 ANSWER 4 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2004:231967 BIOSIS
DOCUMENT NUMBER: PREV200400231888
TITLE: **RT-PCR** of **urine** **survivin** and MN/CA9 for non-invasive **diagnosis** of transitional cell **carcinoma** (TCC) of urinary **bladder**.
AUTHOR(S): Li, G. [Reprint Author]; Passebosc-Faure, K.; Gentil-Perret, A.; Lambert, C.; Genin, C.; Tostain, J. [Reprint Author]
CORPORATE SOURCE: Department of Urology - Andrology, CHU Saint Etienne, Saint Etienne, France
SOURCE: European Urology Supplements, (February 2004) Vol. 3, No. 2, pp. 98. print.
Meeting Info.: 19th Congress of the European Association of Urology. Vienna, Austria. March 24-27, 2004. European Association of Urology.
ISSN: 1569-9056 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 28 Apr 2004
Last Updated on STN: 28 Apr 2004

L11 ANSWER 5 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN

ACCESSION NUMBER: 2004-088235 [09] WPIDS
DOC. NO. CPI: C2004-035873
TITLE: Predicting recurrence of tumor or cancer in human comprises **quantifying** populations of **labeled** ribonucleic acid, and calculating ratio of the amounts of **Survivin** ribonucleic acid and pro-apoptosis factor ribonucleic acid.
DERWENT CLASS: B04
INVENTOR(S): SANDLER, A D
PATENT ASSIGNEE(S): (IOWA) UNIV IOWA RES FOUND
COUNTRY COUNT: 1
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG

US 6656684	B1 20031202 (200409)*	16

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
US 6656684	B1	US 2000-705146	20001102

PRIORITY APPLN. INFO: US 2000-705146 20001102
AN 2004-088235 [09] WPIDS
AB US 6656684 B UPAB: 20040205
NOVELTY - Predicting recurrence of tumor or cancer in human comprises contacting RNA from human physiological sample, with **Survivin**-specific oligonucleotide and pro-apoptosis factor (PAF)-specific oligo-nucleotide; **quantifying** populations of **labeled** RNA; and calculating the ratio of the amounts of **Survivin** RNA and PAF RNA.

DETAILED DESCRIPTION - Predicting the recurrence of a tumor or cancer in a human comprises contacting RNA from a human physiological sample suspected of being tumorigenic or cancerous with a **Survivin**-specific oligonucleotide comprising a first **label**, and a PAF-specific oligo-nucleotide comprising a second **label** under conditions effective to **hybridize** the RNA to the oligonucleotides to yield a first population of RNA **labeled** with the **Survivin** -specific oligonucleotide and a second population of RNA **labeled** with the PAF-specific oligo-nucleotide; **quantifying** the first and second populations of **labeled** RNA to **determine** an amount of **Survivin** RNA and an amount of PAF RNA present in the sample; and calculating the ratio of the amount of **Survivin** RNA and the amount of PAF RNA. A **Survivin**:PAF ratio of more than about 1.5 is predictive that the tumor will recur.

USE - For predicting the recurrence of a tumor or cancer in a human.

ADVANTAGE - The **Survivin**:Fas ratio is a powerful predictor of recurrent disease, and assists in guiding treatment, counseling and follow-up therapeutic strategies with patients having tumors. In particular, **Survivin**:Fas ratio of greater than 1.5, preferably greater than 2, is highly sensitive and specific predictor of tumor recurrence.

DESCRIPTION OF DRAWING(S) - The figure shows a comparative chart for the **Survivin**:Fas ration calculated from RPA values for normal **kidney**, non-recurrent **tumors**, and recurrent **tumors**.

Dwg.4/7

L11 ANSWER 6 OF 38 MEDLINE on STN DUPLICATE 2
ACCESSION NUMBER: 2003535595 IN-PROCESS
DOCUMENT NUMBER: PubMed ID: 14613989
TITLE: Recursive partitioning as an approach to selection of immune markers for tumor **diagnosis**.
AUTHOR: Koziol James A; Zhang Jian-Ying; Casiano Carlos A; Peng Xuan-Xian; Shi Fu-Dong; Feng Anne C; Chan Edward

K L; Tan Eng M
CORPORATE SOURCE: Division of Biomathematics, The Scripps Research Institute, La Jolla, California 92037, USA.
CONTRACT NUMBER: CA56956 (NCI)
RR00833 (NCRR)
SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2003 Nov 1) 9 (14) 5120-6.
Journal code: 9502500. ISSN: 1078-0432.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: IN-PROCESS; NONINDEXED; Priority Journals
ENTRY DATE: Entered STN: 20031118
Last Updated on STN: 20031219

AB PURPOSE AND EXPERIMENTAL DESIGN: Cancer **sera** contain antibodies which react with a unique group of autologous cellular antigens called tumor-associated antigens (TAAs), but the low frequency of positive reactions against any individual antigen has precluded use of autoantibodies as useful **diagnostic** markers. With **enzyme immunoassay**, we examined antibody frequencies to a panel of seven TAAs, c-myc, cyclin B1, IMP1, Koc, p53, p62, and **survivin**, in 527 **cancer** patients (64 **breast cancer** patients, 45 **colorectal cancers**, 91 gastric **cancers**, 65 hepatocellular **carcinomas**, 56 **lung cancers**, and 206 **prostate cancers**), and 346 normals. We used recursive partitioning to assess whether we could accurately classify individuals as either cancer patients or normals on the basis of the profile of antibody reactivity to the seven TAAs for each individual. RESULTS: Recursive partitioning resulted in the selection of subsets of the seven-panel TAA, which differentiated between tumors and controls, and these subsets were unique to each cancer cohort. The classification trees had sensitivities ranging from 0.77 to 0.92 and specificities ranging from 0.85 to 0.91 in the cancer cohorts when normal means +2 SDs were used as standard cutoffs for **immunoassay** positivity. Antibody to cyclin B1 was the initial discriminating node for gastric and **lung cancers**, and for hepatocellular **carcinoma**, and was a subsequent discriminating node in all of the other **cancer** cohorts. c-myc was the initial discriminating node in **breast cancer**, p62 in **prostate cancer**, and IMP1 in colon **cancer** . Recursive partitioning demonstrated that no more than three of the seven TAAs were needed for any cancer cohort to arrive at these levels of sensitivity and specificity. CONCLUSIONS: This initial study shows that multiple antigen miniarrays can provide accurate and valuable tools for cancer **detection** and **diagnosis**. Performance of the miniarrays might be enhanced by other combinations of TAAs appropriately selected for different cancer cohorts.

L11 ANSWER 7 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2003325794 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12855648
TITLE: Therapeutic targeting of the **survivin**

pathway in cancer: initiation of mitochondrial apoptosis and suppression of tumor-associated angiogenesis.

AUTHOR: Blanc-Brude Olivier P; Mesri Mehdi; Wall Nathan R; Plescia Janet; Dohi Takehiko; Altieri Dario C

CORPORATE SOURCE: Department of Cancer Biology and the Cancer Center, University of Massachusetts Medical School, Worcester, Massachusetts 01605, USA.

CONTRACT NUMBER: CA78810 (NCI)
CA90917 (NCI)
HL 54131 (NHLBI)

SOURCE: Clinical cancer research : an official journal of the American Association for Cancer Research, (2003 Jul) 9 (7) 2683-92.
Journal code: 9502500. ISSN: 1078-0432.

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200404
ENTRY DATE: Entered STN: 20030713
Last Updated on STN: 20040421
Entered Medline: 20040420

AB PURPOSE: Molecular antagonists of the inhibitor of apoptosis protein **survivin** have shown promise as novel anticancer strategies for triggering tumor cell apoptosis, dysregulating mitotic progression, and inhibiting tumor growth in preclinical models. However, how **survivin** couples to the cell death machinery has remained elusive, and the relevant cellular targets of **survivin** antagonists have not been completely elucidated. Experimental Design: Human umbilical vein and dermal microvascular endothelial cells were infected with replication-deficient adenoviruses encoding **survivin** (pAd-**Survivin**), green fluorescent protein (pAd-GFP), or a phosphorylation-defective **survivin** Thr(34)-->Ala (pAd-T34A) dominant negative mutant. The effect of wild-type or mutant **survivin** was investigated on capillary network stability, endothelial cell viability, and caspase activation in vitro and on kinetics of **tumor** growth and development of angiogenesis in a **breast cancer** xenograft model in vivo. The cell death pathway initiated by **survivin** targeting was mapped with respect to cytochrome c release, changes in mitochondrial transmembrane potential, and apoptosome requirements using mouse embryonic fibroblasts deficient in Apaf-1 or caspase-9. RESULTS: Adenoviral transduction of endothelial cells with pAd-**Survivin** inhibited growth factor deprivation- or ceramide-induced apoptosis, reduced caspase-3 and -7 generation, and stabilized three-dimensional capillary networks in vitro. Conversely, expression of pAd-T34A caused apoptosis in umbilical vein and dermal microvascular endothelial cells and resulted in caspase-3 activity. Cell death induced by **survivin** targeting exhibited the hallmarks of mitochondrial-dependent apoptosis with release of cytochrome c and loss of mitochondrial transmembrane potential and was suppressed in Apaf-1 or caspase-9 knockout mouse embryonic fibroblasts. When injected in human **breast cancer** xenografts, pAd-T34A inhibited

growth of established **tumors** and triggered **tumor** cell apoptosis in vivo. This was associated with a approximately 60% reduction in tumor-derived **blood** vessels by **quantitative** morphometry of CD31-stained tumor areas, and appearance of endothelial cell apoptosis by internucleosomal DNA fragmentation in vivo. CONCLUSIONS: **Survivin** functions as a novel upstream regulator of mitochondrial-dependent apoptosis, and molecular targeting of this pathway results in anticancer activity via a dual mechanism of induction of tumor cell apoptosis and suppression of angiogenesis.

L11 ANSWER 8 OF 38 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:911201 SCISEARCH
THE GENUINE ARTICLE: 732TP
TITLE: Influence of COX-2 inhibition by rofecoxib on **serum** and tumor progastrin and gastrin levels and expression of PPAR gamma and apoptosis-related proteins in gastric cancer patients
AUTHOR: Konturek P C; Konturek S J (Reprint); Bielanski W; Kania J; Zuchowicz M; Hartwich A; Rehfeld J F; Hahn E G
CORPORATE SOURCE: Univ Med Coll, Dept Physiol, Ul Grzegorzecka 16, PL-31531 Krakow, Poland (Reprint); Univ Erlangen Nurnberg, Dept Med, Erlangen, Germany; Jagiellonian Univ, Coll Med, Dept Physiol, Krakow, Poland; Dist Hosp, Dept Surg, Krakow, Poland; Univ Copenhagen, Rigshosp, Dept Clin Biochem, DK-2100 Copenhagen, Denmark
COUNTRY OF AUTHOR: Poland; Germany; Denmark
SOURCE: DIGESTIVE DISEASES AND SCIENCES, (OCT 2003) Vol. 48, No. 10, pp. 2005-2017.
Publisher: KLUWER ACADEMIC/PLENUM PUBL, 233 SPRING ST, NEW YORK, NY 10013 USA.
ISSN: 0163-2116.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 41

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB Cyclooxygenase-2 (COX-2) expression and certain growth hormones, such as gastrin, have been related to gastric carcinogenesis, but little is known about the factors that enhance this COX-2 expression and whether specific blockade of this **enzyme** has any influence on tumor growth and progression. Our objective was to **determine** the influence of a specific COX-2 inhibitor, rofecoxib (Vioxx), on **serum** and tumor levels of gastrin and its precursor, progastrin, as well as on tumor gene expression of COX-2, peroxisome proliferator-activated receptor gamma (PPARgamma), and apoptosis-related proteins (Bax and Bcl-2, caspase-3, and **survivin**). Twenty-four gastric cancer (GC) patients entered this study and were examined twice, once before and then following a 14-day treatment with Vioxx at a dose of 25 mg twice daily. For comparison, 48 age- and sex-matched healthy controls and 24 similarly matched Helicobacter pylori (Hp)-positive subjects were enrolled and treated with Vioxx as GC patients. **Serum** levels of anti-Hp and anti-CagA antibodies as well as

IL-8 and TNF-alpha were **measured** by **enzyme** -linked immunosorbent **assay** (**ELISA**), while **serum** and tumor contents of progastrin and amidated gastrin were **determined** by specific RIA. Tumor gene and protein expressions of COX-2, PPARgamma, Bax and Bcl-2, caspase-3, and **survivin** were **determined** by **RT-PCR** and western blot. The overall Hp and CagA seropositivity in 24 GC patients was significantly higher (82% and 47%) than in 48 controls (61% and 22%) but not in 24 Hp-infected subjects (100% and 38%). **Serum** IL-8 and TNF-alpha values were significantly higher in GC patients than in controls without GC or Hp-infected controls. Median **serum** progastrin and gastrin levels were found to be significantly higher in GC than in controls without GC and in Hp-positive subjects. Treatment of GC patients with Vioxx resulted in a significant decrease in **plasma** and tumor contents of both progastrin and gastrin, and this was accompanied by the increment in tumor expression of COX-2, PPARgamma, Bax, and caspase-3 with a concomitant reduction in Bcl-2 and **survivin** expression. We conclude that: (1) GC patients show significantly higher Hp and CagA seropositivity than age- and sex-matched controls, but not Hp-positive subjects, indicating that infection with cytotoxic Hp is linked to GC. (2) **Serum** progastrin and gastrin levels are signficantly higher in GC patients than in matched controls, confirming that both gastrins may be implicated in gastric carcinogenesis. 3) GC patients exhibit significantly higher levels of IL-8 and TNF-alpha than non-GC controls and Hp-positive subjects, probably reflecting more widespread gastritis in GC. (4) COX-2, PPARgamma, Bcl-2, and **survivin** were overexpressed in gastric tumor, but the inhibition of COX-2 activity by Vioxx resulted in a significant reduction in **serum** and tumor levels of progastrin and gastrin and **serum** IL-8 and TNF-alpha levels, suggesting that gastrin and proinflammatory cytokines could mediate the up-regulation of COX-2 in gastric cancerogenesis. (5) Vioxx also enhanced expression of COX-2, PPARgamma, Bax, and caspase-3, while inhibiting the expression of Bcl-2 and **survivin**, suggesting that COX-2 blockade might be useful in chemoprevention against gastric cancer possibly due to enhancement of the PPARgamma- and proapoptotic proteins-dependent apoptosis and the reduction in progastrin/gastrin-induced promotion of tumor growth.

L11 ANSWER 9 OF 38 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004215796 EMBASE
TITLE: **Detection** of **survivin** in exfoliate cell in **urine**.
AUTHOR: Pu X.; Chen Y.; Wang Z.; Fu S.; Lu J.; Shi T.; Ma B.
CORPORATE SOURCE: X. Pu, Department of Urology Institute, 2nd Hosp. of Lanzhou Medical College, Lanzhou 730030 Gansu Province, China. puxy2000@yahoo.cm
SOURCE: Chinese Journal of Clinical Rehabilitation, (2003) 7/8 (1276-1277).
Refs: 9
ISSN: 1671-5926 CODEN: ZLKHAH
COUNTRY: China
DOCUMENT TYPE: Journal; Article

FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
LANGUAGE: Chinese
SUMMARY LANGUAGE: English; Chinese
AB Aim. To develop a method that can early **diagnose** and routine **screen** out **bladder cancer**, but it does not impair patients by **detecting survivin** in exfoliate cell in **urine** of patients with **bladder cancer**. Methods. 200 ml fresh **urine** of 31 patients with **bladder cancer** and 20 patients with other benign urinary diseases and 10 healthy volunteers who voided the second **urine** in morning was **detected** the expression of the **survivin** by **RT-PCR**. Results. The sensentivity(100%) **detecting** the **survivin** in the **urine** by **RT-PCR** is markedly higher than the sensitivity of **urine** cytology($P < 0.01$). Conclusion. **Detecting survivin** in the **urine** is a simple noninvasive method and can be used in **diagnosing** blader **cancer** .

L11 ANSWER 10 OF 38 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003251695 EMBASE
TITLE: **Detection** of anti-livin antibody in gastrointestinal cancer patients.
AUTHOR: Yagihashi A.; Asanuma K.; Tsuji N.; Torigoe T.; Sato N.; Hirata K.; Watanabe N.
CORPORATE SOURCE: N. Watanabe, Dept. of Clin. Laboratory Medicine, Sapporo Med. Univ. Sch. of Medicine, South-1, West-16, Chuo-ku, Sapporo 060-8543, Japan. watanabn@sapmed.ac.jp
SOURCE: Clinical Chemistry, (1 Jul 2003) 49/7 (1206-1208). Refs: 11
ISSN: 0009-9147 CODEN: CLCHAU
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 016 Cancer
029 Clinical Biochemistry
048 Gastroenterology
LANGUAGE: English

L11 ANSWER 11 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2004:153341 BIOSIS
DOCUMENT NUMBER: PREV200400148069
TITLE: RNA-transfected CD40-activated B cells generate functional T cell responses against viral and tumor antigen targets: Implications for immuno-gene therapy in pediatric patients.
AUTHOR(S): Coughlin, Christina M. [Reprint Author]; Vance, Barbara A. [Reprint Author]; Grupp, Stephan A.; Vonderheide, Robert H. [Reprint Author]
CORPORATE SOURCE: Abramson Family Cancer Research Institute, University of Pennsylvania School of Medicine, Philadelphia, PA, USA

SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 744a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB Vaccination with antigen-presenting cells (APC) engineered to mimic mechanisms of immune stimulation represents a promising approach for cancer immunotherapy. Dendritic cell (DC) vaccines have entered phase III testing in adult malignancies, but application in pediatric patients has been challenging, with adequate numbers of DC difficult to collect from smaller patients, even with leukapheresis. Here, we evaluate RNA-transfected CD40-activated B lymphocytes (CD40-B) as a novel gene therapy approach to an APC vaccine with potent T cell stimulatory capacity and the ability to be generated from small **blood** volumes without use of vectors or viruses. Using tumor-derived RNA as the antigenic payload permits targeting of multiple antigens, a particularly important issue in pediatric oncology (and many adult tumors) where few tumor-associated antigens have been described. From starting **blood** volumes of 4-8 cc, we generated >100 million CD40-B from pediatric oncology patients in 4-week cultures (n=10). These cells expressed high levels of MHC, costimulatory and adhesion molecules and could be electroporated with mRNA at >80% efficiency based on transfection with mRNA for green fluorescent protein (GFP). For two model antigens (influenza matrix protein FluMP and the melanoma antigen MART-1), RNA-transfected CD40-B induced in vitro cytotoxic T cells (CTL) from adults and children that **labeled** with peptide/MHC tetramers, specifically secreted IFN-gamma in ELISPOT **assays**, and killed tumor cells in an antigen-specific and MHC-restricted fashion. Comparable induction of CTL against both antigens was obtained with RNA-loaded DC. To **determine** whether CD40-B can induce anti-tumor CTL without targeting a particular tumor antigen during in vitro priming, we electroporated CD40-B cells from high-risk **neuroblastoma** (NBL) patients (n=3, mean age 2.3 years old) with total tumor RNA derived from three NBL cell lines. CTL induced in these experiments killed NBL cell lines in an MHC-restricted fashion, including NBL lines not used for preparing tumor RNA. Moreover, CD40-B electroporated with total RNA from autologous NBL cells induced anti-tumor CTL that lysed NBL cells in an MHC-restricted manner. CTL induced with GFP mRNA or autologous lymphocyte RNA did not lyse tumor cells or autologous CD40-B. Interestingly, up to 4% of CD8+ CTL in these cultures **labeled** with tetramers specific for the widely expressed tumor antigen **survivin**, indicating that multiple antigens, both known and unknown, can be simultaneously targeted with this approach. These findings suggest that both small patient size and the paucity of defined tumor antigens in pediatric oncology can be overcome by CD40-B/RNA technology.

L11 ANSWER 12 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2004:151475 BIOSIS
DOCUMENT NUMBER: PREV200400147509
TITLE: IGF-II (IGF-2) is a major proliferative/anti-apoptotic cytokine and a therapeutic target in MM, other hematologic neoplasias and solid tumors.
AUTHOR(S): Mitsiades, Constantine S. [Reprint Author]; Mitsiades, Nicholas [Reprint Author]; McMullan, Ciaran J. [Reprint Author]; Rung, Andrew L.; Anderson, Kenneth C. [Reprint Author]
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Dept. of Medical Oncology, Dana-Farber Cancer Institute, Harvard Med. School, Boston, MA, USA
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 593a-594a. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 17 Mar 2004
Last Updated on STN: 17 Mar 2004

AB We have previously shown (Oncogene 2002;21:5673, PNAS 2002;99:14374; **Blood** 2002;100s:) that inhibition of the kinase activity of insulin-like growth factor-1 receptor (IGF-1R/CD221) significantly suppresses proliferation, survival and attenuates the drug resistance of tumor cells from multiple myeloma (MM), other hematologic malignancies and solid tumors. We have also shown that the biologic activity of insulin-like growth factors (IGFs) present in **serum** is sufficient to stimulate IGF-1R kinase activity. So far, the study of ligands for IGF-1R has focused primarily on IGF-1 (mainly due to its high levels and prominent role in growth during childhood). However, we hypothesized that IGF-II may also be a critical regulator of tumor cell proliferation and survival. We therefore used specific anti-IGF-I and anti-IGF-II neutralizing antibodies (Ab), to selectively abrogate the biologic activity of each of these cytokines, and dissect their relative effects on tumor cells cultured with **serum** (fetal bovine, from healthy donors or MM patients). We confirmed that saturating concentrations of anti-IGF-II neutralizing Ab significantly suppressed proliferation/survival of freshly isolated MM cells from drug-resistant patients; 40 MM cell lines (including cells resistant to a conventional or novel drugs); and cell lines from various subtypes of leukemias, lymphomas, and solid **tumors** (e.g. **breast, prostate, lung,** colon, thyroid, ovarian, **renal** Ca, retinoblastoma, sarcoma). IGF-II neutralization generally had more pronounced effect than anti-IGF-I neutralizing Ab, while combined neutralization of both cytokines had effect comparable to IGF-IR inhibition. **ELISA assays detected** significantly higher levels of IGF-II than IGF-I in a cohort of 20 MM patient **sera**

tested, (x+/-SD 795+/-153 vs 181+/-74 ng/mL, respectively, p<0.05). Because IGF-1R does not exhibit kinase activity in the absence of ligand(s) binding, these findings indicate that a major component of the biologic activity of IGF-1R signaling in malignant cells may be triggered by IGF-II. We therefore studied the gene expression and proteomic profiling of IGF-II stimulation of tumor cells, and conversely, further explored the biologic effects of IGF-II inhibition. We found that physiological levels of IGF-II stimulate pleiotropic proliferative/anti-apoptotic molecular events, including activation of key growth/survival pathways (e.g. PI-3K/Akt, Ras/Raf/MAPK, IKK-alpha/NF-kappaB); increased expression of inhibitors of apoptosis (e.g. FLIP, XIAP, cIAP-2, **survivin**); neutralization of pro-apoptotic Forkhead transcription factors; stimulation of proteasome and telomerase activity; as well as enhanced proliferative response of tumor cells to other growth factors (e.g. MM or PrCa cells to IL-6). Conversely, IGF-II neutralization partially inhibits the protective effect of **serum** against Dex, chemotherapeutics or PS-341 or the protection of BMSCs on MM cells; attenuates MM cell responses to IL-6; and suppresses VEGF production by tumor cells (e.g. MM, prostate or thyroid Ca) or bone marrow stromal cells. These studies document that IGF-II, plays a major role in tumor cell proliferation/survival, and that IGF-I levels in cancer patients are not the sole **determinant** of the activity of IGFs/IGF-1R signaling cascade. Our results also indicate that comprehensive suppression of the biological activity of both IGF-I and IGF-II is desirable, in order to neutralize the biological activity of this system and its pleiotropic effects in conferring resistance to diverse anti-tumor agents.

L11 ANSWER 13 OF 38 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN

ACCESSION NUMBER: 2004056039 EMBASE
TITLE: Dynamic changes of specific T cell responses to melanoma correlate with IL-2 administration.
AUTHOR: Andersen M.H.; Gehl J.; Reker S.; Pedersen L.O.; Becker J.C.; Geertsen P.; Thor Straten P.
CORPORATE SOURCE: P. Thor Straten, Tumor Immunology Group, Danish Cancer Society, 2100 Copenhagen, Denmark. ps@cancer.dk
SOURCE: Seminars in Cancer Biology, (2003) 13/6 (449-459). Refs: 46
ISSN: 1044-579X CODEN: SECBE7
COUNTRY: United Kingdom
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 013 Dermatology and Venereology
016 Cancer
026 Immunology, Serology and Transplantation
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Interleukin 2 (IL-2) is a promising immunotherapeutic agent for the treatment of metastatic melanoma and **renal** cell **carcinoma**. Systemic administration of high dose IL-2 produces objective responses in up to 25% of melanoma patients, and

a low but significant proportion of these patients experience durable responses. Nevertheless, the cells and molecules responsible for induction of **tumor** regression over the course of IL-2 treatment remain unknown. New strategies in **tumor** immunotherapy have evolved over the past decade as a consequence of significant progress in the field, in particular with respect to the characterization of peptide epitopes derived from **tumor** associated antigens, and the role of antigen presenting cells in the initiation of cellular immune responses. Alongside with these factual as well as conceptual advances, new methods have been developed to **monitor** and characterize anti-**tumor** T cell responses in **cancer** patients. Application of these tools to dissect anti-**tumor** responses has demonstrated that various immune therapeutic approaches can induce powerful systemic anti-**tumor** cytotoxic T lymphocyte (CTL) responses. However, only limited efforts have been made to use present days tool to analyze anti-**tumor** immune responses in patients treated with IL-2 based immunotherapy. We have examined CTL responses against known **tumor** antigens in melanoma patients over the course of IL-2 based immunotherapy (electrochemotherapy). Surprisingly, anti-**tumor** CTL responses significantly declined upon initiation of therapy, but reappeared when IL-2 administration was paused. Molecular analyses of the clonotypic composition of responding T cells demonstrated that new clones emerged over the course of treatment, and that **tumor**-specific T cells that had left the peripheral **blood** could subsequently be **detected** at the **tumor** site. These data provide new insight into the biological actions of IL-2 and highlight the difficulties associated with the **monitoring** of anti-**tumor** immune responses. This underlines the importance of frequent sampling of **blood** and **tumor** biopsies to be analyzed with a combination of state of the art technologies in order to gain detailed information on the interactions between **cancer** cells and cells of the immune system.

L11 ANSWER 14 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2003:451505 BIOSIS
DOCUMENT NUMBER: PREV200300451505
TITLE: Expression of the apoptosis inhibitor **survivin** down-regulates Caspase 3 activity in human **bladder cancer** cell lines.
AUTHOR(S): Lyrakos, Nikolaos [Reprint Author]; Elyan, Sean; Warner, Phil; Woodman, Anthony
CORPORATE SOURCE: Cranfield University at Silsoe, Silsoe, UK
SOURCE: Proceedings of the American Association for Cancer Research Annual Meeting, (July 2003) Vol. 44, pp. 415. print.
Meeting Info.: 94th Annual Meeting of the American Association for Cancer Research. Washington, DC, USA. July 11-14, 2003.
ISSN: 0197-016X.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)

LANGUAGE: English
ENTRY DATE: Entered STN: 1 Oct 2003
Last Updated on STN: 1 Oct 2003

L11 ANSWER 15 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2004:110250 BIOSIS
DOCUMENT NUMBER: PREV200400108397
TITLE: New directions in the treatment of mesothelioma.
AUTHOR(S): Stahel, R. [Reprint Author]
CORPORATE SOURCE: Department of Oncology, Universitatsspital Zurich, Zurich, Switzerland
SOURCE: EJC Supplements, (September 2003) Vol. 1, No. 5, pp. S317. print.
Meeting Info.: 12th ECCO (European Cancer Conference). Copenhagen, Denmark. September 21-25, 2003. Federation of European Cancer Societies.
ISSN: 1359-6349 (ISSN print).
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 25 Feb 2004
Last Updated on STN: 25 Feb 2004

L11 ANSWER 16 OF 38 MEDLINE on STN
ACCESSION NUMBER: 2003286478 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12796695
TITLE: Effect of intravesical treatment of transitional cell carcinoma with bacillus Calmette-Guerin and mitomycin C on urinary **survivin** levels and outcome.
AUTHOR: Hausladen Derek A; Wheeler Marcia A; Altieri Dario C; Colberg John W; Weiss Robert M
CORPORATE SOURCE: Department of Surgery, Section of Urology, Yale University School of Medicine, PO Box 208041 YPB-3, New Haven, CT 06520-8041, USA.
CONTRACT NUMBER: DK 38311 (NIDDK)
DK 47548 (NIDDK)
SOURCE: Journal of urology, (2003 Jul) 170 (1) 230-4.
Journal code: 0376374. ISSN: 0022-5347.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals
ENTRY MONTH: 200307
ENTRY DATE: Entered STN: 20030620
Last Updated on STN: 20030710
Entered Medline: 20030709

AB PURPOSE: **Urine survivin** is a predictive/**prognostic** molecular marker that **detects** transitional cell carcinoma (TCC) with high specificity and sensitivity. The presence of **urine survivin** in patients with TCC who receive intravesical instillation of bacillus Calmette-Guerin or mitomycin C may predict recurrence. MATERIALS AND METHODS: **Urine** from 25 subjects receiving 27 intravesical treatments of bacillus Calmette-Guerin or mitomycin C for TCC were collected prior to, during and after treatment.

Urinary **survivin** levels were compared with outcome, as assessed by cytology and cystoscopy with or without biopsy 1 month and up to 12 months after the completion of treatment. RESULTS: Pretreatment **survivin** levels were higher in subjects in whom TCC recurred following treatment compared with those who achieved remission. **Survivin** levels increased several-fold during treatment with the highest **survivin** levels **measured** in subjects with recurrence. Median posttreatment values of **survivin** were zero in those who achieved remission and 1.0 ng/ml **urine** in subjects in whom TCC recurred. CONCLUSIONS: The presence of urinary **survivin** 1 month after the completion of treatment predicts TCC recurrence with 100% sensitivity and 78% specificity. Specificity to predict TCC recurrence increases to 92% after 1 year. No TCC recurred for 1 year in 12 of the 14 subjects with a posttreatment **survivin** level of 0.1 ng or less per ml **urine**. Three of the 4 subjects who were **survivin** positive but in remission 1 month after the completion of treatment had recurrent TCC within 1 year. Subjects who have urinary **survivin** after the completion of intravesical instillation have a high likelihood of TCC recurrence.

L11 ANSWER 17 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2003:232382 BIOSIS
DOCUMENT NUMBER: PREV200300232382
TITLE: Evaluation of **survivin reverse transcriptase polymerase chain** reaction (**RT-PCR**) for non-invasive **detection** of **bladder cancer**.
AUTHOR(S): Moussa, Omar M. [Reprint Author]; el-Enin, Hassan Abou; Bissada, Nabil K.; Ghoneim, Mohamed A.; Watson, Dennis K.
CORPORATE SOURCE: Charleston, SC, USA
SOURCE: Journal of Urology, (April 2003) Vol. 169, No. 4 Supplement, pp. 226. print.
Meeting Info.: 98th Annual Meeting of the American Urological Association (AUA). Chicago, IL, USA. April 26-May 01, 2003. American Urological Association.
CODEN: JOURAA. ISSN: 0022-5347.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 May 2003
Last Updated on STN: 14 May 2003

L11 ANSWER 18 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2004:168570 BIOSIS
DOCUMENT NUMBER: PREV200400162264
TITLE: Analysis of **survivin** mRNA expression, and Fas ligand and GM-CSF concentrations in the pediatric patients with acute leukemias.
AUTHOR(S): Jung, Hye Lim [Reprint Author]; Choi, Jaewon [Reprint Author]; Yoo, Keon Hee [Reprint Author]; Kim, Dong

Hyun [Reprint Author]; Sung, Ki Woong [Reprint Author]; Koo, Hong Hoe [Reprint Author]; Lee, Mark
CORPORATE SOURCE: Pediatrics, Sungkyunkwan University School of Medicine, Seoul, South Korea
SOURCE: Blood, (November 16 2003) Vol. 102, No. 11, pp. 224b. print.
Meeting Info.: 45th Annual Meeting of the American Society of Hematology. San Diego, CA, USA. December 06-09, 2003. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 24 Mar 2004
Last Updated on STN: 24 Mar 2004

AB **Survivin**, a member of the inhibitor of apoptosis family, is expressed in a cell-cycle-dependent manner in all the most common human cancers but not in normal differentiated adult tissues. It suppresses apoptosis induced by Fas, Bax, caspases and anticancer drugs. **Survivin** is considered as potential unfavorable **prognostic** factor in many solid tumors, acute myeloid leukemia (AML), and adult T-cell leukemia. Fas ligand (FasL) function as apoptotic mediators, and GM-CSF was shown to increase surviving expression in AML cell lines. We investigated **survivin** mRNA expression, concentrations of FasL and GM-CSF in newly **diagnosed** pediatric AML and acute lymphoblastic leukemias (ALL), and analyzed their correlations with clinical and laboratory **prognostic** features exhibited at **diagnosis**, and early marrow response. **Survivin** mRNA expressions were **quantified** by real time PCR **assay** in 54 bone marrow (BM) samples collected from 15 AML and 39 ALL patients at initial **diagnosis**. FasL and GM-CSF concentrations were **quantified** by **ELISA** **assay** in **serum** collected from same patients at initial **diagnosis**. We analyzed relationship between **survivin** m-RNA expression and FasL and GM-CSF concentrations. We also analyzed relationships between **survivin** m-RNA expression and age at **diagnosis**, initial WBC count, induction day 7 (ALL) marrow status, or event (AML), statistically. High **survivin** expression was **detected** in all AML and ALL samples compared to normal adult lymphocytes. When **survivin** expression was compared to lung adenocarcinoma cell line A549, 9 of 15 AML samples and 38 of 39 ALL samples expressed higher. The **quantified** mean values of **survivin** expression were statistically higher in ALL than AML (30.89 versus 13.07, $P<0.0005$). **Survivin** expression was not different between 21 high-risk group and 18 standard-risk group ALL patients. There were no significant correlations between **survivin** expression and age, initial WBC count, induction day 7 (ALL) marrow status, or event (AML), statistically. The mean concentrations of FasL in AML, standard risk-group ALL, and high-risk group ALL were 128.16, 194.17, and 249.44 pg/mL, respectively. The mean concentrations of GM-CSF in AML, standard-risk group ALL, and high-risk group ALL were 13.23, 5.50, and 3.89 pg/mL, respectively. No significant correlations were observed between **survivin** expression and FasL or

GM-CSF concentrations. We conclude that **survivin** expression may play an important role in the oncogenesis of AML and ALL in pediatric age. We could not show significance of **survivin** expression as **prognostic** marker in childhood AML and ALL. We also could not find relationship between surviving and FasL or GM-CSF in childhood acute leukemias.

L11 ANSWER 19 OF 38 MEDLINE on STN DUPLICATE 3
ACCESSION NUMBER: 2003071087 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12582023
TITLE: Enhancement of antibody **detection** in cancer using panel of recombinant tumor-associated antigens.
AUTHOR: Zhang Jian-Ying; Casiano Carlos A; Peng Xuan-Xian; Koziol James A; Chan Edward K L; Tan Eng M
CORPORATE SOURCE: W.M. Keck Autoimmune Disease Center, The Scripps Research Institute, La Jolla, California 92037, USA.
CONTRACT NUMBER: CA56956 (NCI)
SOURCE: Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology, (2003 Feb) 12 (2) 136-43. Journal code: 9200608. ISSN: 1055-9965.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE) (MULTICENTER STUDY)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200305
ENTRY DATE: Entered STN: 20030214
Last Updated on STN: 20030531
Entered Medline: 20030530

AB Cancer **sera** contain antibodies which react with a unique group of autologous cellular antigens called tumor-associated antigens (TAAs). This study **determines** whether a mini-array of multiple TAAs would enhance antibody **detection** and be a useful approach to cancer **detection** and **diagnosis**. The mini-array of TAAs comprised full-length recombinant proteins expressed from cDNAs encoding c-myc, p53, cyclin B1, p62, Koc, IMP1, and **survivin**. **Enzyme immunoassay** was used to **detect** antibodies in 527 **sera** from six different types of cancer. Antibody frequency to any individual TAA was variable but rarely exceeded 15-20%. With the successive addition of TAAs to a final total of seven antigens, there was a stepwise increase of positive antibody reactions up to a range of 44-68%. **Breast**, **lung**, and **prostate cancer** patients showed separate and distinct profiles of reactivity, suggesting that uniquely constituted antigen mini-arrays might be developed to distinguish between some types of **cancer**. Distinct antibody profiles were not observed in gastric, **colorectal**, and hepatocellular **carcinomas** with this set of seven TAAs. **Detection** of autoantibodies in cancer can be enhanced by using a mini-array of several TAAs as target antigens. Additional studies in early cancer patients and high-risk individuals and the design of unique antigen panels for different cancers would help to **determine** whether multiple antigen mini-arrays for the

detection of autoantibodies might contribute a clinically useful noninvasive approach to cancer **detection** and **diagnosis**.

L11 ANSWER 20 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:232054 BIOSIS
DOCUMENT NUMBER: PREV200300232054
TITLE: **Detection** of **survivin** in **urine** is a powerful marker for the non-invasive **diagnosis** of **bladder cancer**.
AUTHOR(S): Shariat, Shahrokh [Reprint Author]; Casella, Roberto; Hernandez, Gina; Sulser, Tullio; Gasser, Thomas C.; Lerner, Seth P.
CORPORATE SOURCE: Dallas, TX, USA
SOURCE: Journal of Urology, (April 2003) Vol. 169, No. 4 Supplement, pp. 129. print.
Meeting Info.: 98th Annual Meeting of the American Urological Association (AUA). Chicago, IL, USA. April 26-May 01, 2003. American Urological Association.
CODEN: JOURAA. ISSN: 0022-5347.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 14 May 2003
Last Updated on STN: 14 May 2003

L11 ANSWER 21 OF 38 EMBASE COPYRIGHT 2004 ELSEVIER INC. ALL RIGHTS RESERVED. on STN
ACCESSION NUMBER: 2003317756 EMBASE
TITLE: Current **bladder cancer** tests: Unnecessary or beneficial?.
AUTHOR: Simon M.A.; Lokeshwar V.B.; Soloway M.S.
CORPORATE SOURCE: Dr. M.S. Soloway, Department of Urology, Univ. of Miami School of Medicine, PO Box 016960 (M814), Miami, FL 33101, United States. msoloway@miami.edu
SOURCE: Critical Reviews in Oncology/Hematology, (1 Aug 2003) 47/2 (91-107).
Refs: 145
ISSN: 1040-8428 CODEN: CCRHEC
COUNTRY: Ireland
DOCUMENT TYPE: Journal; General Review
FILE SEGMENT: 016 Cancer
028 Urology and Nephrology
036 Health Policy, Economics and Management
037 Drug Literature Index
LANGUAGE: English
SUMMARY LANGUAGE: English
AB **Bladder cancer** is currently **diagnosed** using cystoscopy and cytology in patients with suspicious signs and symptoms. These same tests are used to **monitor** patients with a history of **bladder cancer** for recurrence. The recurrence rate for **bladder cancer** is high, thus necessitating long-term follow-up. **Urine** cytology requires an experienced cytopathologist and is costly. It has high

specificity, but low sensitivity for low-grade **bladder tumors**. Recently many non-invasive **bladder cancer** tests, utilizing markers found in the **urine**, have been developed. The FDA has approved several of these for the use is **bladder cancer diagnosis**, and many others are undergoing development and investigation. An ideal **bladder cancer** test would be non-invasive, highly sensitive and specific, inexpensive, easy to perform, and yield highly reproducible results. Many of the tests reviewed meet some, but not all, of these criteria. .COPYRGT. 2003 Published by Elsevier Ireland Ltd.

L11 ANSWER 22 OF 38 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:151838 SCISEARCH
THE GENUINE ARTICLE: 643XG
TITLE: Ribozyme-mediated cleavage of the human **survivin** mRNA and inhibition of antiapoptotic function of **survivin** in MCF-7 cells
AUTHOR: Choi K S; Lee T H; Jung M H (Reprint)
CORPORATE SOURCE: Natl Inst Hlth, Div Metab Dis, Dept Biomed Sci, Eunpyung Gu, 5 Nokbun Dong, Seoul 122701, South Korea (Reprint); Natl Inst Hlth, Div Metab Dis, Dept Biomed Sci, Eunpyung Gu, Seoul 122701, South Korea; Pusan Natl Univ, Div Nat Sci, Dept Microbiol, Kumjung Gu, Pusan 609735, South Korea
COUNTRY OF AUTHOR: South Korea
SOURCE: CANCER GENE THERAPY, (FEB 2003) Vol. 10, No. 2, pp. 87-95.
Publisher: NATURE PUBLISHING GROUP, MACMILLAN BUILDING, 4 CRINAN ST, LONDON N1 9XW, ENGLAND.
ISSN: 0929-1903.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 50

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Survivin** is a new member of the inhibitor of apoptosis protein (IAP) family that is implicated in the control of cell proliferation and the regulation of cell life span. This protein is selectively expressed in most human **carcinomas** but not in normal adult tissues. To down-regulate a human **survivin** expression as a strategy for **cancer** gene therapy, we designed two hammerhead ribozymes (RZ-1, RZ-2) targeting human **survivin** mRNA. RZ-1 and RZ-2 efficiently cleaved the human **survivin** mRNA at nucleotide positions +279 and +289, which was identified by in vitro cleavage **assay** using in vitro transcribed ribozymes and truncated **survivin** mRNA substrate. To investigate the function of the ribozymes in cells, the sequences of the ribozymes were cloned into replication -deficient adenoviral vector and transferred to **breast cancer** cell, MCF-7. The infection with adenovirus encoding the ribozymes resulted in a significant reduction of **survivin** mRNA (74% and 73%, respectively) and protein. As revealed by nuclear condensation/ fragmentation and flow cytometry analysis, inhibition of **survivin** gene by ribozymes increased apoptosis and sensitivity induced by etoposide or

serum starvation. Our results suggest that the designed hammerhead ribozymes against **survivin** mRNA are good candidates for feasible gene therapy in the treatment of **cancer**.

L11 ANSWER 23 OF 38 SCISEARCH COPYRIGHT 2004 THOMSON ISI on STN
ACCESSION NUMBER: 2003:34426 SCISEARCH
THE GENUINE ARTICLE: 626KH
TITLE: Expression of the anti-apoptotic gene **survivin** in myelodysplastic syndrome
AUTHOR: Badran A; Yoshida A (Reprint); Wano Y; Mutoh M; Imamura S; Yamashita T; Tsutani H; Inuzuka M; Ueda T
CORPORATE SOURCE: Fukui Med Univ, Dept Internal Med 1, Fukui 9101193, Japan (Reprint); Fukui Med Univ, Dept Chem, Fukui 9101193, Japan; Kanazawa Med Univ, Dept Internal Med, Div Hematol & Immunol, Kanazawa, Ishikawa, Japan; Toray Industries Ltd, Basic Res Labs, Kanagawa, Japan
COUNTRY OF AUTHOR: Japan
SOURCE: INTERNATIONAL JOURNAL OF ONCOLOGY, (JAN 2003) Vol. 22, No. 1, pp. 59-64.
Publisher: PROFESSOR D A SPANDIDOS, 1, S MERKOURI ST, EDITORIAL OFFICE,, ATHENS 116 35, GREECE.
ISSN: 1019-6439.
DOCUMENT TYPE: Article; Journal
LANGUAGE: English
REFERENCE COUNT: 28

ABSTRACT IS AVAILABLE IN THE ALL AND IALL FORMATS

AB **Survivin** is a member of the inhibitor of apoptosis protein (IAPs) family and considered to play a pivotal role in oncogenesis. We present the first report of **survivin** expression profile in myelodysplastic syndrome (MDS). Expression of **survivin** messenger RNA was evaluated by semi-**quantitative reverse transcriptase**-**polymerase chain** reaction (**RT**-**PCR**) in patients with MDS and acute myeloid leukemia (AML). Eleven out of 12 patients with refractory anemia (RA) (91.6%), and all 3 patients with refractory anemia with excess blasts in transformation (RAEBt) (100%), were positive for **survivin** expression with the majority of cases showing abundant levels of the **survivin** transcript. On the other hand, expression of **survivin** was undetectable in the 4 patients with chronic myelomonocytic leukemia (CMMoL). The level and frequency of **survivin** expression in patients with refractory anemia were compared to those in patients with AML. Out of 12 patients with de novo AML, 5 patients (41.7%) showed **detectable** levels of **survivin** expression. Abundant **survivin** expression in RA was also confirmed by immunohistochemistry. In contrast, **survivin** was almost absent in two cases with aplastic anemia. We propose that high levels of **survivin** expression can serve as a reliable **diagnostic** marker of RA. in MDS.

L11 ANSWER 24 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2002-590775 [63] WPIDS
DOC. NO. NON-CPI: N2002-468745
DOC. NO. CPI: C2002-167229

TITLE: **Diagnosing, prognosis,** or **monitoring cancer** in a patient, particularly **genitourinary** tract **cancer** e.g. **prostate** or **bladder cancer,** comprises **assaying** a sample of biological **fluid** from a patient for the presence of **survivin.**

DERWENT CLASS: B04 D16 J04 S03

INVENTOR(S): ALTIERI, D C; MORRIS, V A; PLESCIA, J; SMITH, S D; WEISS, R M; WHEELER, M A

PATENT ASSIGNEE(S): (ALTI-I) ALTIERI D C; (MORR-I) MORRIS V A; (PLES-I) PLESCIA J; (SMIT-I) SMITH S D; (WEIS-I) WEISS R M; (WHEE-I) WHEELER M A; (UYYA) UNIV YALE

COUNTRY COUNT: 101

PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2002057787	A2	20020725	(200263)*	EN	41
RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZM ZW					
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CO CR CU CZ DE DK DM DZ EC EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ OM PH PL PT RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VN YU ZA ZM ZW					
US 2002160395	A1	20021031	(200274)		
EP 1350114	A2	20031008	(200370)	EN	
R: AL AT BE CH CY DE DK ES FI FR GB GR IE IT LI LT LU LV MC MK NL PT RO SE SI TR					
AU 2002246970	A1	20020730	(200427)		

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2002057787	A2	WO 2002-US574	20020111
US 2002160395	A1 Provisional	US 2001-260898P	20010112
		US 2002-42302	20020111
EP 1350114	A2	EP 2002-714720	20020111
		WO 2002-US574	20020111
AU 2002246970	A1	AU 2002-246970	20020111

FILING DETAILS:

PATENT NO	KIND	PATENT NO
EP 1350114	A2 Based on	WO 2002057787
AU 2002246970	A1 Based on	WO 2002057787

PRIORITY APPLN. INFO: US 2001-260898P 20010112; US 2002-42302 20020111

AN 2002-590775 [63] WPIDS

AB WO 200257787 A UPAB: 20021001

NOVELTY - **Diagnosing** (M1) cancer in a patient comprising

assaying a sample of biological fluid from a patient for the presence of **survivin**, is new.

DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for:

(1) a kit for **diagnosis**, **prognosis**, or **monitoring** cancer comprising a container for collecting biological fluid from a patient, and an agent that **detects** the presence of **survivin** in the biological fluid;

(2) **determining** the grade and stage of a cancer in a patient by **determining** the amount of **survivin** in the sample of a biological fluid from a patient, and comparing the amount of **survivin** in the sample with that in the control; and

(3) **monitoring** cancer in a patient by **determining** the amount of **survivin** in the biological sample of biological fluid from the patient.

USE - (M1) is useful for **diagnosing**, **detecting**, **prognosing**, **monitoring**, and **determining** the stage and grade of **cancer**, such as **genitourinary** tract **cancer** including **bladder**, **prostate** and **renal cancer**.

ADVANTAGE - The **urine survivin** test is a quick and inexpensive method for **monitoring** patients, and can be integrated in a battery of **urine** markers to improve the sensitivity and specificity of early **detection** of recurrences of cancer.

Dwg.0/4

L11 ANSWER 25 OF 38 MEDLINE on STN DUPLICATE 4

ACCESSION NUMBER: 2003010606 MEDLINE
DOCUMENT NUMBER: PubMed ID: 12516962
TITLE: Multiplex gene expression analysis for high-throughput drug discovery: **screening** and analysis of compounds affecting genes overexpressed in cancer cells.
AUTHOR: Johnson Paul H; Walker Roger P; Jones Steven W; Stephens Kathy; Meurer Janet; Zajchowski Deborah A; Luke May M; Eeckman Frank; Tan Yuping; Wong Linda; Parry Gordon; Morgan Thomas K Jr; McCarrick Meg A; Monforte Joseph
CORPORATE SOURCE: Department of Cancer Research, Berlex Biosciences, Richmond, California 94804-0099, USA.. JohnsonPaulH@att.net
SOURCE: Molecular cancer therapeutics, (2002 Dec) 1 (14) 1293-304.
Journal code: 101132535. ISSN: 1535-7163.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200306
ENTRY DATE: Entered STN: 20030109
Last Updated on STN: 20030619
Entered Medline: 20030618

AB Drug discovery strategies are needed that can rapidly exploit

multiple therapeutic targets associated with the complex gene expression changes that characterize a polygenic disease such as cancer. We report a new cell-based high-throughput technology for **screening** chemical libraries against several potential cancer target genes in parallel. Multiplex gene expression (MGE) analysis provides direct and **quantitative measurement** of multiple endogenous mRNAs using a multiplexed **detection** system coupled to **reverse transcription-PCR**. A multiplex **assay** for six genes overexpressed in **cancer** cells was used to **screen** 9000 chemicals and known drugs in the human **prostate cancer** cell line PC-3. Active compounds that modulated gene expression levels were identified, and IC50 values were **determined** for compounds that bind DNA, cell surface receptors, and components of intracellular signaling pathways. A class of steroids related to the cardiac glycosides was identified that potently inhibited the **plasma** membrane Na(+)K(+)-ATPase resulting in the inhibition of four of the prostate target genes including transcription factors Hoxb-13, hPSE/PDEF, hepatocyte nuclear factor-3alpha, and the inhibitor of apoptosis, **survivin**. Representative compounds selectively induced apoptosis in PC-3 cells compared with the nonmetastatic cell line BPH-1. The multiplex **assay** distinguished potencies among structural variants, enabling structure-activity analysis suitable for chemical optimization studies. A second multiplex **assay** for five toxicological markers, Hsp70, Gadd153, Gadd45, O6-methylguanine-DNA methyltransferase, and cyclophilin, **detected** compounds that caused DNA damage and cellular stress and was a more sensitive and specific indicator of potential toxicity than **measurement** of cell viability. MGE analysis facilitates rapid drug **screening** and compound optimization, the simultaneous **measurement** of toxicological end points, and gene function analysis.

L11 ANSWER 26 OF 38 JICST-EPlus COPYRIGHT 2004 JST on STN
ACCESSION NUMBER: 1030876597 JICST-EPlus
TITLE: **Detection** of Urinary **Survivin** Gene in **Bladder Cancer** Patients
AUTHOR: SATO ERINA; IRIE AKIRA; SATO TAKEFUMI; MIZOGUCHI HIDEYUKI; TSUMURA HIDEYASU; BABA SHIRO
UCHIDA TOYOAKI
TOYOOKA YUKO; YAMABE HARUMI
CORPORATE SOURCE: Kitasato Univ., Hosp.
Tokaidai Hachiojibyoin Hinyokika
Kitasato Univ., Hosp.
SOURCE: Kitasato Igaku (Kitasato Medicine), (2002) vol. 32, no. 5, pp. 385-390. Journal Code: Z0070A (Fig. 2, Tbl. 2, Ref. 15)
ISSN: 0385-5449
PUB. COUNTRY: Japan
DOCUMENT TYPE: Journal; Article
LANGUAGE: Japanese
STATUS: New
AB **Survivin** is an inhibitor of apoptosis that is selectively overexpressed in common human **cancers**, but not in normal tissues, and this overexpression correlates with aggressive disease

and unfavorable outcomes. To investigate the potential suitability of **survivin** gene **detection** in **urine** as a novel predictive molecular marker of **bladder cancer**, 19 patients with **bladder cancer** and 12 control patients were analyzed by **reverse transcriptase polymerase chain** reaction (**RT-PCR**). **Survivin** was **detected** in the urinary samples of 15.8% (3/19) of the patients with **bladder cancer** but not in the control group. Patients with **survivin** positive showed a poor **prognosis** compared to control group (p=0.0525, Kaplan-Meier method). Staging (p=0.0130) and **survivin** (p=0.0220) showed a statistically significant difference with **prognosis** by Stepwise regression analysis. **Determination** of urinary **survivin** may be useful te identify the **prognosis** for patients with **bladder cancer**. (author abst.)

L11 ANSWER 27 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN

ACCESSION NUMBER: 2002:444088 BIOSIS
DOCUMENT NUMBER: PREV200200444088
TITLE: Urinary **survivin** testing to **monitor bladder cancer** burden in patients receiving intravesical chemotherapy.
AUTHOR(S): Hausladen, Derek A. [Reprint author]; Wheeler, Marcia A. [Reprint author]; Colberg, John W. [Reprint author]; Altieri, Dario C. [Reprint author]; Weiss, Robert M. [Reprint author]
CORPORATE SOURCE: New Haven, CT, USA
SOURCE: Journal of Urology, (April, 2002) Vol. 167, No. 4 Supplement, pp. 162. print.
Meeting Info.: Annual Meeting of the American Urology Association, Inc. Orlando, Florida, USA. May 25-30, 2002.
CODEN: JOURAA. ISSN: 0022-5347.
DOCUMENT TYPE: Conference; (Meeting)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 21 Aug 2002
Last Updated on STN: 21 Aug 2002

L11 ANSWER 28 OF 38 MEDLINE on STN DUPLICATE 5

ACCESSION NUMBER: 2002179987 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11815300
TITLE: **Bladder cancer detection** with urinary **survivin**, an inhibitor of apoptosis.
AUTHOR: Sharp Jennifer D; Hausladen Derek A; Maher M Grey; Wheeler Marcia A; Altieri Dario C; Weiss Robert M
CORPORATE SOURCE: Department of Surgery (Section of Urology), Yale University School of Medicine, New Haven, Connecticut 06520, USA.
SOURCE: Frontiers in bioscience : a journal and virtual library, (2002 Feb 1) 7 e36-41. Ref: 56
Journal code: 9709506. ISSN: 1093-4715.

Searcher : Shears 571-272-2528

PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200206
ENTRY DATE: Entered STN: 20020401
Last Updated on STN: 20020606
Entered Medline: 20020605

AB The current "gold standard" for the **diagnosis** of **bladder cancer** is cystoscopy and **urine** cytology. Cystoscopy, a naked eye assessment of the bladder, is invasive, uncomfortable and costly while cytology has high specificity but low sensitivity (40-60%) particularly for low-grade lesions. Therefore, there is a need for a molecular tumor marker **assay** that is simple to perform and sensitive, particularly for low-grade lesions. By looking to the pathophysiology of **bladder cancer**, we identified **survivin**, an inhibitor of apoptosis that is not generally expressed in fully differentiated adult tissue and is highly expressed in **bladder cancer**. **Survivin** is **detected** in whole **urine** of patients with TCC using a simple antibody based test. The sensitivity of **survivin** testing for new or recurrent **bladder cancer** is 100% while the specificity for other **neoplastic** and non-**neoplastic genitourinary** disease is 95%. The high sensitivity of this simple, noninvasive test is well suited to **bladder cancer**, a disease with high rates of recurrence.

L11 ANSWER 29 OF 38 BIOSIS COPYRIGHT 2004 BIOLOGICAL ABSTRACTS INC. on STN
ACCESSION NUMBER: 2003:356612 BIOSIS
DOCUMENT NUMBER: PREV200300356612
TITLE: The IGF/IGF-1R System Is a Major Therapeutic Target for Multiple Myeloma, Other Hematologic Malignancies and Solid Tumors.
AUTHOR(S): Mitsiades, Constantine S. [Reprint Author]; Mitsiades, Nicholas [Reprint Author]; Kung, Andrew L. [Reprint Author]; Shringapurne, Reshma [Reprint Author]; Poulaki, Vassiliki [Reprint Author]; Richardson, Paul G. [Reprint Author]; Liberman, Towia A. [Reprint Author]; Munshi, Nikhil C. [Reprint Author]; Loukopoulos, Dimitris [Reprint Author]; Anderson, Kenneth C. [Reprint Author]
CORPORATE SOURCE: Jerome Lipper Multiple Myeloma Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA
SOURCE: Blood, (November 16 2002) Vol. 100, No. 11, pp. Abstract No. 637. print.
Meeting Info.: 44th Annual Meeting of the American Society of Hematology. Philadelphia, PA, USA. December 06-10, 2002. American Society of Hematology.
CODEN: BLOOAW. ISSN: 0006-4971.
DOCUMENT TYPE: Conference; (Meeting)

Conference; (Meeting Poster)
Conference; Abstract; (Meeting Abstract)
LANGUAGE: English
ENTRY DATE: Entered STN: 6 Aug 2003
Last Updated on STN: 6 Aug 2003

AB We and others have shown that insulin-like growth factors (IGFs) stimulate proliferation of multiple myeloma (MM) cells and protect them from apoptosis by e.g. Dex or Apo2L/TRAIL. We now show that the IGF/IGF-1 receptor (IGF-1R/CD221) pathway represents a major therapeutic target for MM cells and other neoplasias. We studied a panel of 25 MM cell lines, including cells resistant to Dex, anthracyclines, thalidomide (Thal), immunomodulatory Thal derivatives (IMiDs), Apo2L/TRAIL; 30 **tumor** samples from MM patients, including patients resistant to IMiDs or PS-341; as well as 30 cell lines from a wide range of hematologic malignancies, including B- and T-ALL, AML, CML, various non-Hodgkin's lymphoma (NHL) subtypes and solid **tumors** (e.g. **breast, prostate, lung** (SCLC and NSCLC), thyroid, ovarian, **renal** Ca, retinoblastoma). All tumor cell lines and 10/10 MM patient samples tested strongly expressed surface IGF-1R. To **determine** if endogenous IGF levels can sufficiently trigger tumor cell growth/survival, we studied if the proliferative/anti-apoptotic effect of **serum** (fetal bovine, pooled **sera** from healthy donors or autologous **sera** from MM patients) can be blunted by specifically inhibiting IGF-1R using an anti-IGF-1R neutralizing monoclonal antibody (mAb); an IGF-1-like peptide which binds to IGF-1R without activating its Tyr kinase activity, and competitively inhibits IGF-1R activation; and the small molecule specific IGF-1R tyrosine kinase inhibitor, ADW (Novartis AG, Basel, Switzerland). We also compared the impact of IGF-1R vs IL-6R inhibition, using specific anti-IL-6R neutralizing mAb. All 3 IGF-1R-inihibitory molecules profoundly suppressed the ability of **serum** to promote the growth/survival of MM and all other (with the exception of NHL) cell lines (in 5, 10% or 20% FBS or pooled human **sera**) and MM patient tumor cells (20% FBS or autologous **serum** from BM aspirates) (after 24, 48 and 72-hour cultures) (median reduction of total MM cell survival by 70%). IL-6R inhibition had minimal, if any, effect on the **serum**-induced growth/survival of MM cell lines or patient cells (with notable exception of modest inhibition in MM-1S cells). All 3 anti-IGF-1R strategies exhibited comparable anti-MM effects. ADW also had in vivo anti-tumor activity in a SCID/NOD mice model of diffuse MM. Mechanistic studies showed that IGF-1R inhibition blocks key growth/survival pathways (e.g. PI-3K/Akt, Ras/Raf/MAPK, IKK-alpha/NF-kappaB); blocks expression of several inhibitors of apoptosis (e.g. FLIP, XIAP, cIAP-2, **survivin**); increases PS-341-sensitivity of MM cells; and suppresses both constitutive and **serum**- or IGF-1-induced upregulation of proteasome activity and telomerase activity. Our studies a) show that IGF-1R plays a major role in growth/survival of a wide range of human neoplasias; b) indicate that IGF-1R can be targeted with multiple clinically applicable approaches; and therefore c) provide proof-of-principle for blockade of IGF/IGF-1R in human neoplasias, and, in particular, for clinical trials of the IGF-1R Tyr kinase inhibitor ADW, for patients with MM, a disease particularly dependent upon the IGF-1R function.

L11 ANSWER 30 OF 38 WPIDS COPYRIGHT 2004 THOMSON DERWENT on STN
ACCESSION NUMBER: 2001-483146 [52] WPIDS
DOC. NO. CPI: C2001-144852
TITLE: **Detecting** abnormal cellular proliferations, e.g. neoplastic or hyperplastic cellular growth or proliferation by **determining** (over)expression of nucleic acid or protein products of **survivin** gene in bodily substances.
DERWENT CLASS: B04 D16
INVENTOR(S): CHAN, R C K; JOUBEN-STEELE, L; NICHOLS, W S
PATENT ASSIGNEE(S): (CEDA-N) CEDARS SINAI MEDICAL CENT
COUNTRY COUNT: 93
PATENT INFORMATION:

PATENT NO	KIND	DATE	WEEK	LA	PG
WO 2001053535	A2	20010726	(200152)*	EN	29

RW: AT BE CH CY DE DK EA ES FI FR GB GH GM GR IE IT KE LS LU MC MW MZ NL OA PT SD SE SL SZ TR TZ UG ZW
W: AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH CN CR CU CZ DE DK DM DZ EE ES FI GB GD GE GH GM HR HU ID IL IN IS JP KE KG KP KR KZ LC LK LR LS LT LU LV MA MD MG MK MN MW MX MZ NO NZ PL PT RO RU SD SE SG SI SK SL TJ TM TR TT TZ UA UG UZ VN YU ZA ZW

AU 2001031025	A	20010731	(200171)

APPLICATION DETAILS:

PATENT NO	KIND	APPLICATION	DATE
WO 2001053535	A2	WO 2001-US1956	20010119
AU 2001031025	A	AU 2001-31025	20010119

FILING DETAILS:

PATENT NO	KIND		PATENT NO
AU 2001031025	A	Based on	WO 2001053535

PRIORITY APPLN. INFO: US 2000-488191 20000120
AN 2001-483146 [52] WPIDS
AB WO 200153535 A UPAB: 20010914
NOVELTY - **Detecting** a neoplastic, hyperplastic, cytologically dyplastic and/or premalignant cellular growth or proliferation in a human subject comprises **determining** (over)expression of nucleic acid or protein products of **survivin** gene, which is **detected** in bodily substances.

DETAILED DESCRIPTION - **Detecting** a neoplastic, hyperplastic, cytologically dyplastic and/or premalignant cellular growth or proliferation in a human subject comprises:

(a) collecting a sample of a bodily substance containing human nucleic acid from the human subject;

(b) amplifying a **Survivin**-encoding mRNA in the sample

to form **survivin**-specific amplification products using **survivin**-specific primers selected from (i-iv):

(i) SR1F: tcttggaggg ctgcgcctgc; SR2R: agtctggctc gttctcagtg g; SRP: cagtggatga agccagcctc; SRVF1: ccctttctca aggaccaccg; SRVR2: actgggccaa gtctggctcg; and SRTP: ccgaggctgg cttcatccac tgc;

(ii) a nucleotide sequence complementary to (i);

(iii) a **survivin** gene-specific fragment of (i) or (ii) that is at least 15 nucleotides long;

(iv) or a **survivin** gene-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions of any of the sequence (i) or (ii) at its 5' or 3' end; and

(c) **detecting** the presence or absence of expression of a human **survivin** gene in the bodily substance by analyzing the amplification products. The presence of **survivin**-specific amplification products is **diagnostic** for the presence of neoplastic, hyperplastic, cytologically dyplastic and/or premalignant cellular growth or proliferation in the human subject.

INDEPENDENT CLAIMS are also included for the following:

(1) a **survivin** gene-specific oligonucleotide primer or probe comprising (i)-(iv) above;

(2) an oligonucleotide primer set for amplifying a **survivin** gene-specific nucleic acid segment, comprising at least a forward primer and at least a reverse primer, where:

(a) the forward primer is a nucleic acid comprising:

(i) SR1F or SRVF1;

(ii) a nucleotide sequence complementary to SR1F or SRVF1;

(iii) a gene-specific fragment of (i) or (ii) that is at least 15 nucleotides long; or

(iv) a **survivin** gene-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions of (i) or (ii) at its 5' or 3' end; and

(b) the reverse primer comprises:

(i) SR2R, SRP or SRVR2;

(ii) a nucleotide sequence complementary to any of (i);

(iii) a **survivin** gene-specific fragment of (i) or (ii) that is at least 15 nucleotides long; or

(iv) a **survivin** gene-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions of any sequence of (i) or (ii) at its 5' or 3' end;

(3) an oligonucleotide primer set for amplifying a **survivin** gene-specific nucleic acid segment comprising at least a forward primer and at least a reverse primer, where:

(a) the forward primer is a nucleic acid comprising:

(i) SRTP;

(ii) a nucleotide sequence complementary to (i);

(iii) a gene-specific fragment of (i) or (ii) that is at least 15 nucleotides long; or

(iv) a **survivin** gene-specific nucleotide sequence overlapping at 5 or more contiguous nucleotide positions of any sequence of (i) or (ii) at its 5' or 3' end; and

(b) a reverse primer comprises:

(i) SR2R or SRVR2;

(ii) a nucleotide sequence complementary to any one of (i);

(iii) a survivin gene-specific fragment of (i) or (ii) that is at least 15 nucleotide long; or